

**Chronic Chest Pain—High Probability of Coronary Artery Disease
EVIDENCE TABLE**

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
1. Di Fiore DP, Beltrame JF. Chest pain in patients with 'normal angiography': could it be cardiac? <i>Int J Evid Based Healthc.</i> 2013;11(1):56-68.	Review/Other-Dx	N/A	To provide a brief overview of the important clinical considerations in this common presentation and particularly focus on coronary vasomotor disorders (ie, those involving an inappropriate vasoconstriction or impaired vasodilation) that need to be considered.	No results stated in abstract.	4
2. McKavanagh P, Lusk L, Ball PA, et al. A comparison of Diamond Forrester and coronary calcium scores as gatekeepers for investigations of stable chest pain. <i>Int J Cardiovasc Imaging.</i> 2013;29(7):1547-1555.	Observational-Dx	250 patients	To determine if calcium scores (CS) could act as a more effective gatekeeper than Diamond Forrester (DF) in the assessment of patients with suspected coronary artery disease (CAD).	The mean DF was 47.8 and mean CS 172.5. Of the 144 patients with non-anginal pain 19.4 % had significant disease (>50 % stenosis). In general the DF overestimated the presence of CAD whereas the CS reclassified patients to lower risk groups, with 91 in the high risk DF category compared to 26 in the CS. Both receiver operating curve and McNemar Bowker test analysis suggested the DF was less accurate in the prediction of CAD compared to CS [Formula: see text] Projected downstream investigations were also calculated, with the cost per number of significant stenoses identified cheaper with the CS criteria.	3
3. Versteyleen MO, Joosen IA, Shaw LJ, Narula J, Hofstra L. Comparison of Framingham, PROCAM, SCORE, and Diamond Forrester to predict coronary atherosclerosis and cardiovascular events. <i>J Nucl Cardiol.</i> 2011;18(5):904-911.	Observational-Dx	1296 patients	To study 4 frequently used risk scores in their ability to predict for CAD and major adverse cardiovascular events in patients presenting with stable chest pain at the cardiology outpatient clinic.	Framingham (FRS), PROCAM, SCORE risk score, and Diamond Forrester pre-test probability were calculated. All patients were followed up for a mean 19 +/- 9 months for all cardiovascular events (mortality, acute coronary syndrome, revascularization >90 days after CCTA). In ROC-analysis for prediction of significant CAD, the AUC for FRS; 0.68 (95% CI: 0.64–0.72) and for SCORE; 0.69 (95% CI: 0.65–0.72) were significantly higher than for PROCAM; 0.64 (95% CI: 0.61-0.68; $P \leq 0.001$), as well as marginally higher than for Diamond Forrester; 0.65 (95% CI: 0.61–0.68; $P \leq 0.05$). Low FRS category showed the lowest number of patients with significant CAD, compared to patients with low risk using PROCAM, SCORE or Diamond Forrester ($P < .001$). Also, low FRS category showed less events (compared to PROCAM and SCORE; $P < .001$, for Diamond Forrester; $P = .14$).	3

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4. Wasfy MM, Brady TJ, Abbara S, et al. Comparison of the Diamond-Forrester method and Duke Clinical Score to predict obstructive coronary artery disease by computed tomographic angiography. <i>Am J Cardiol.</i> 2012;109(7):998-1004.	Observational-Dx	114 patients	To evaluate the ability of the Diamond and Forrester method (DFM) and the Duke Clinical Score (DCS) to predict obstructive coronary artery disease (CAD) on coronary computed tomographic angiography (CCTA) and the effect of these different risk scores on the appropriateness level using the 2010 Appropriate Use Criteria.	The CCTA results were classified as revealing obstructive ($\geq 70\%$ stenosis), nonobstructive ($< 70\%$), or no CAD. When the patients' risk was classified using the DFM, 18% were low, 65% intermediate, and 17% high risk. When using the DCS, 53% of patients had a reclassification of their risk, most of whom changed from intermediate to either low or high risk (50% low, 19% intermediate, 35% high risk). The net reclassification improvement for the prediction of obstructive CAD was 51% ($p = 0.01$). Of the 37 patients who were reclassified as low risk, 36 (97%) lacked obstructive CAD. Appropriateness for CCTA was reclassified for 13% of patients when using the DCS instead of the DFM, and the number of appropriate examinations was significantly fewer (68% vs 55%, $p < 0.001$).	2
5. Margolis JR, Chen JT, Kong Y, Peter RH, Behar VS, Kisslo JA. The diagnostic and prognostic significance of coronary artery calcification. A report of 800 cases. <i>Radiology.</i> 1980;137(3):609-616.	Observational-Dx	800 patients	To evaluate the diagnostic and prognostic significance of coronary artery calcification.	Patients with calcification demonstrated poorer survival at all follow-up intervals (from 6 months to 5 years); the 5-year survival rate was 87% for patients without calcification, compared to 58% for those with calcification. The prognostic significance of coronary artery calcification appears to be independent of information obtained by cardiac catheterization and angiocardiography.	3

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6. Milne EN, Pistolesi M, Miniati M, Giuntini C. The radiologic distinction of cardiogenic and noncardiogenic edema. <i>AJR Am J Roentgenol.</i> 1985;144(5):879-894.	Observational-Dx	216 chest radiographs of 61 patients	To determine, as objectively and rigorously as possible, the validity of the chest radiograph in deciding what type of pulmonary edema is present, in order to provide a rational pathophysiologic basis for the treatment of that particular type of edema.	Three principal and seven ancillary features have been identified, all of which are statistically significant and permit the cause of the edema to be determined correctly in a high percentage of cases. The three principal features are distribution of pulmonary flow, distribution of pulmonary edema, and the width of the vascular pedicle. The ancillary features are pulmonary blood volume, peribronchial cuffing, septal lines, pleural effusions, air bronchograms, lung volume, and cardiac size. Differing constellations of these features occur, each of which is characteristic of a specific type of edema. Overall accuracy of diagnosis in this study ranged from 86% to 89%. The highest accuracy was obtained in distinguishing capillary permeability edema from all other varieties (91%), and the lowest in distinguishing chronic cardiac failure from renal failure (81%).	3
7. Basu S, Senior R, Dore C, Lahiri A. Value of thallium-201 imaging in detecting adverse cardiac events after myocardial infarction and thrombolysis: a follow up of 100 consecutive patients. <i>Bmj.</i> 1996;313(7061):844-848.	Observational-Dx	100 patients	To determine the prognostic role of thallium-201 imaging compared with that of exercise electrocardiography in patients with acute myocardial infarction treated by thrombolysis.	Reversible ischaemia on 201TI imaging predicted adverse cardiac events in 33 out of 37 patients with such events during follow up (hazard ratio 8.1 (95% confidence interval 2.7 to 23.8), $P < 0.001$). Exercise electrocardiography showed reversible ischaemia in 33 patients, of whom 13 had subsequent events, and failed to predict events in 24 patients (hazard ratio 1.1 (0.56 to 2.2), $P = 0.8$).	2
8. Bax JJ, Poldermans D, Elhendy A, Boersma E, Rahimtoola SH. Sensitivity, specificity, and predictive accuracies of various noninvasive techniques for detecting hibernating myocardium. <i>Curr Probl Cardiol.</i> 2001;26(2):147-186.	Meta-analysis	77 articles	To perform a pooled analysis of the currently available studies in the literature to determine and compare the sensitivities, specificities, positive predictive value (PPV), and negative predictive value (NPV) to predict improvement of regional LV function after revascularization) of the 5 most frequently used techniques, namely DE, single photon emission computed tomography (SPECT) using 201TI RR or 201TI RI, 99mTc-labeled sestamibi (MIBI), and positron emission tomography (PET) with FDG.	The current analysis demonstrated that all techniques have a higher NPV/sensitivity compared with their PPV/specificity. Both pooled analyses of all available data and direct comparisons demonstrated that higher sensitivities/NPVs are obtained with nuclear imaging, whereas higher specificities/PPVs are obtained with DE.	M

* See Last Page for Key

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<p>9. Beller GA. Diagnostic accuracy of thallium-201 myocardial perfusion imaging. <i>Circulation</i>. 1991;84(3 Suppl):11-6.</p>	<p>Review/Other-Dx</p>	<p>N/A</p>	<p>To review the diagnostic accuracy of thallium-201 myocardial perfusion imaging including the factors affecting sensitivity and specificity.</p>	<p>Myocardial thallium-201 (Tl-201) imaging performed in conjunction with exercise stress has enhanced the accuracy of detecting coronary artery disease among patients with chest pain. Sensitivity and specificity of qualitative visual Tl-201 scintigraphy for detection of coronary artery disease average 84% and 87%, respectively. Quantitative analysis of planar Tl-201 scintigrams has yielded sensitivity and specificity in the 90% range. Single photon emission computed tomographic imaging is associated with even higher sensitivity but with specificity in the 82-85% range. Perfusion defects representing ischemia can now be distinguished from scar by demonstration of delayed Tl-201 redistribution or enhanced uptake after reinjection of a second dose of Tl-201. Stenoses of the left circumflex coronary artery are less easily detected than lesions of the right and left anterior descending coronary arteries. False-positive Tl-201 perfusion defects may occur as a result of attenuation artifacts, most often caused by overlying breast tissue or by a high left hemidiaphragm. Patient motion during acquisition of single photon emission computed tomographic images results in artifactual defects on reconstruction. Abnormal Tl-201 uptake has been noted in patients with 1) left bundle branch block and normal coronary arteries, 2) hypertrophic cardiomyopathy, and 3) progressive systemic sclerosis.</p>	<p>4</p>

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10. Christian TF, Miller TD, Bailey KR, Gibbons RJ. Noninvasive identification of severe coronary artery disease using exercise tomographic thallium-201 imaging. <i>Am J Cardiol.</i> 1992;70(1):14-20.	Observational-Dx	688 patients	To provide clinically useful noninvasive predictions of the likelihood of the presence of significant left main or 3-vessel CAD, using clinical, exercise and tomographic thallium imaging variables in a large patient cohort.	Logistic regression analysis identified 4 variables as independently predictive of left main or 3-vessel CAD. These variables were the magnitude of ST-segment depression with exercise, the number of visually abnormal short-axis thallium-201 segments, the presence or absence of diabetes mellitus, and the change in systolic blood pressure with exercise. Using these variables, patients were classified by nomograms into low-, intermediate- and high-probability groups. Patients at high probability (n = 205) had a 52% prevalence of 3-vessel or left main CAD, whereas those at low probability (n = 170) had only a 12% prevalence. Only 53 patients (29%) with 3-vessel or left main CAD had perfusion abnormalities in all 3 coronary territories.	3

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11. Gibbons RJ. Rest and exercise radionuclide angiography for diagnosis in chronic ischemic heart disease. <i>Circulation</i> . 1991;84(3 Suppl):193-99.	Review/Other-Dx	N/A	To review several issues critical to the current understanding of the use of radionuclide angiography.	Rest and exercise radionuclide angiography is frequently employed for the diagnosis of chest pain syndromes. Its value and limitations in this regard have been well studied, but proper utilization of the technique requires an understanding of five critical concepts: 1) Radionuclide angiography is superior to treadmill exercise testing and probably equivalent to thallium scintigraphy, although the published series did not use current methods. 2) The true specificity of radionuclide angiography is about 80%, intermediate between the early optimistic estimates and the later pessimistic ones. 3) The peak exercise ejection fraction is the preferred test parameter for diagnosis, although exercise hemodynamics, symptoms, and electrocardiographic changes should also be considered. 4) Although radionuclide angiography is clearly helpful for noninvasive diagnosis, significant numbers of patients will continue to fall in an uncertain category. 5) The proper application of the technique requires recognition of its limitations and careful attention to technical details. When properly applied, this modality can make an important contribution to clinical decision making.	4

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12. Giri S, Shaw LJ, Murthy DR, et al. Impact of diabetes on the risk stratification using stress single-photon emission computed tomography myocardial perfusion imaging in patients with symptoms suggestive of coronary artery disease. <i>Circulation</i> . 2002;105(1):32-40.	Observational-Dx	4,755 patients	To evaluate the incremental role of stress single-photon emission computed tomography (SPECT) imaging in diabetic patients in the prediction of cardiac events.	Of 4755 patients, 929 (19.5%) were diabetic. Patients with diabetes, despite an increased revascularization rate, had 80 cardiac events (8.6%; 39 deaths and 41 MIs) compared with 172 cardiac events (4.5%; 69 deaths and 103 MIs) in the nondiabetic cohort (P<0.0001). Abnormal stress MPI was an independent predictor of cardiac death and MI in both populations. Diabetics with ischemic defects had an increased number of cardiac events (P<0.001), with the highest MI rates (17.1%) observed with 3-vessel ischemia. Similarly, a multivessel fixed defect was associated with the highest rate of cardiac death (13.6%) among diabetics. The unadjusted cardiac survival rate was lower for diabetic patients (91% versus 97%, P<0.001), but it became comparable once adjusted for the pretest clinical risk and stress MPI results. In multivariable Cox analysis, both ischemic and fixed MPI defects independently predicted cardiac death alone or cardiac death/MI. Diabetic women had the worst outcome for any given extent of myocardial ischemia.	2
13. Meine TJ, Hanson MW, Borges-Neto S. The additive value of combined assessment of myocardial perfusion and ventricular function studies. <i>J Nucl Med</i> . 2004;45(10):1721-1724.	Review/Other-Dx	N/A	To focus on the combined assessment of myocardial perfusion and left ventricular function.	Two clear roles for nuclear imaging in clinical practice include the diagnosis of coronary artery disease and assessment of prognosis in patients with known coronary artery disease. Ventricular function information can help differentiate an attenuation artifact from an infarct and is helpful in diagnosing 3-vessel coronary disease. Additionally, several studies have highlighted the prognostic benefit to combined assessment of myocardial perfusion and ventricular function. Several new modalities have recently been reported that promise to continue to solidify the place of nuclear imaging in the diagnosis and prognosis of coronary artery disease.	4

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14. Soman P, Taillefer R, DePuey EG, Udelson JE, Lahiri A. Enhanced detection of reversible perfusion defects by Tc-99m sestamibi compared to Tc-99m tetrofosmin during vasodilator stress SPECT imaging in mild-to-moderate coronary artery disease. <i>J Am Coll Cardiol.</i> 2001;37(2):458-462.	Observational-Dx	88 patients	To compare dipyridamole single-photon emission computed tomography (SPECT) imaging with Tc-99m sestamibi and Tc-99m tetrofosmin for the detection of reversible perfusion defects in patients with mild-to-moderate coronary artery disease.	Tc-99m sestamibi detected reversible perfusion defects in a greater number of segments (total 363 and 285, $p < 0.001$, and mean \pm SD, 2.2 \pm 3.0 and 1.8 \pm 2.5 per patient, $p = 0.008$, for Tc-99m sestamibi and Tc-99m tetrofosmin, respectively), demonstrated a larger extent of perfusion defect (mean \pm SD, 15.8% \pm 12.3% and 12.0% \pm 11.4%, $p < 0.03$, for Tc-99m sestamibi and Tc-99m tetrofosmin, respectively) and more often correctly identified patients with disease in more than one coronary artery ($p = 0.02$). There was better defect contrast with Tc-99m sestamibi (defect/normal wall count ratios were 0.60 \pm 0.15 vs. 0.73 \pm 0.14 for Tc-99m sestamibi and Tc-99m tetrofosmin, respectively, $p = 0.01$, for reversible defects seen in identical segments with both agents; and 0.73 \pm 0.16 vs 0.79 \pm 0.17, respectively, $p < 0.01$, for reversible defects detected with either agent alone). There was no significant difference in diagnostic sensitivity or image quality.	2
15. Taillefer R, DePuey EG, Udelson JE, Beller GA, Latour Y, Reeves F. Comparative diagnostic accuracy of Tl-201 and Tc-99m sestamibi SPECT imaging (perfusion and ECG-gated SPECT) in detecting coronary artery disease in women. <i>J Am Coll Cardiol.</i> 1997;29(1):69-77.	Observational-Dx	115 female patients	To directly compare the sensitivity and specificity of thallium-201 (Tl-201), technetium-99m (Tc-99m) sestamibi perfusion and Tc-99m sestamibi electrocardiographic (ECG)-gated single-photon emission computed tomographic (SPECT) studies for detection of coronary artery disease (CAD).	The overall sensitivities for detecting \geq 50% and \geq 70% stenoses were 75.0% and 84.3%, respectively, for Tl-201, and 71.9% and 80.4%, respectively, for Tc-99m sestamibi perfusion studies ($p = 0.48$). The specificity for lesions \geq 50% was 61.9% for Tl-201 and 85.7% for Tc-99m sestamibi perfusion ($p = 0.07$), whereas for lesions \geq 70% it was 58.8% for Tl-201 and 82.4% for Tc-99m sestamibi perfusion ($p = 0.01$). When the 34 patients with a normal coronary angiogram were added to the group of 30 normal volunteers, the "specificity" for lesions \geq 70% was 67.2% for Tl-201, 84.4% for Tc-99m sestamibi SPECT perfusion ($p = 0.02$) and 92.2% for Tc-99m sestamibi gated SPECT ($p = 0.0004$).	2

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16. Vanzetto G, Ormezzano O, Fagret D, Comet M, Denis B, Machecourt J. Long-term additive prognostic value of thallium-201 myocardial perfusion imaging over clinical and exercise stress test in low to intermediate risk patients : study in 1137 patients with 6-year follow-up. <i>Circulation</i> . 1999;100(14):1521-1527.	Observational-Dx	1,137 patients	To assess, in a large cohort of patients with low- to intermediate-likelihood of future cardiac events, whether the prognostic value of Tl201-SPECT was maintained at long-term follow-up and whether myocardial perfusion imaging was of incremental prognostic value over clinical and ETT data.	Overall mortality was higher after strongly positive (ST depression >2 mm, or >1 mm for a workload <=75 W) (2.36%/y) or nondiagnostic ETT (1.63%/y) than after normal (0.85%/y) or positive ETT (1.37%/y) (P=0.002), and after abnormal SPECT than after normal SPECT (1.60%/y versus 0.68%/y, P=0.001). The major cardiac event rate (cardiac death or myocardial infarction [MI]) was 0.88%, 1.59%, 2.10%, and 2.13%/y after negative, positive, strongly positive, and nondiagnostic ETT, respectively (P=0.003), and 0.56%, 1.43%, and 2.05%/y in patients with 0, 1 to 2, and >=3 abnormal segments on SPECT, respectively (P<0.002). An abnormal SPECT was predictive of MI (P<0.001), whereas ETT was not. In multivariate analysis, SPECT was of incremental prognostic value over clinical and ETT data for predicting overall mortality and major cardiac events.	3
17. Baghdasarian SB, Noble GL, Ahlberg AW, Katten D, Heller GV. Risk stratification with attenuation corrected stress Tc-99m sestamibi SPECT myocardial perfusion imaging in the absence of ECG-gating due to arrhythmias. <i>J Nucl Cardiol</i> . 2009;16(4):533-539.	Observational-Dx	419 patients	To define the role of AC in the risk stratification of patients with SPECT myocardial perfusion imaging studies in patients unable to undergo ECG-gating.	The 419 patients had a mean age of 71.5 +/- 11.7 years and most (70.6%) underwent pharmacologic stress. In follow-up, 35 (8.4%) patients suffered an adverse cardiac event. Patients with AC-SSS 1-3 and AC-SSS 4-8 had similar cardiac event rates (11.4% vs 10.5%, P = NS). Accordingly, AC-SSS cutoffs of 0, 1-8, and >8 were selected to classify perfusion as normal, mildly abnormal, and moderately to severely abnormal with annualized event rates of 2.1%, 10.8%, and 18.7%, respectively (P < .001). In multivariable analysis, AC-SSS >8 was the most powerful predictor of cardiac events followed by AC-SSS 1-8, history of CAD, age >75 and pharmacologic stress.	3

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18. Emmett L, Iwanochko RM, Freeman MR, Barolet A, Lee DS, Husain M. Reversible regional wall motion abnormalities on exercise technetium-99m-gated cardiac single photon emission computed tomography predict high-grade angiographic stenoses. <i>J Am Coll Cardiol.</i> 2002;39(6):991-998.	Observational-Dx	100 patients	To determine the level of angiographic stenosis at which reversible regional wall motion abnormalities (RWMA) are present on exercise stress technetium-99m (Tc-99m)-gated single photon emission computed tomography (SPECT) myocardial perfusion imaging (MPI), and whether assessments of stress and rest RWMA add incremental diagnostic information.	The sensitivity of reversible RWMA for angiographic stenoses >70% was 53%, with a specificity of 100%. The presence of reversible RWMA was able to stratify patients with angiographic stenoses of 50% to 79% and 80% to 99% with a high positive predictive value. A good correlation was noted between the presence of reversible RWMA and the coronary artery jeopardy score (R = 0.49, p < 0.0001). Multivariate analysis showed that the post-stress RWMA, Duke treadmill and reversible RWMA scores were significant predictors of angiographic severity.	2
19. Maddahi J, Kiat H, Van Train KF, et al. Myocardial perfusion imaging with technetium-99m sestamibi SPECT in the evaluation of coronary artery disease. <i>Am J Cardiol.</i> 1990;66(13):55E-62E.	Observational-Dx	278 patients	To review several aspects of myocardial perfusion imaging using Tc-99m sestamibi and SPECT.	The results of the current clinical trials using acquisition and processing parameters similar to those for Tl-201 and a separate (2-day) injection protocol suggest that Tc-99m sestamibi and Tl-201 single photon emission computed tomography (SPECT) provide similar information with respect to detection of myocardial perfusion defects, assessment of the pattern of defect reversibility, overall detection of coronary artery disease (CAD) and detection of disease in individual coronary arteries. Tc-99m sestamibi SPECT appears to be superior to Tc-99m sestamibi planar imaging because the former provides a higher defect contrast and is more accurate for detection of disease in individual coronary arteries.	3
20. Saraste A, Nekolla S, Schwaiger M. Nuclear cardiology needs new "blood". <i>J Nucl Cardiol.</i> 2009;16(2):180-183.	Review/Other-Dx	N/A	N/A	N/A	4

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21. Hachamovitch R, Rozanski A, Hayes SW, et al. Predicting therapeutic benefit from myocardial revascularization procedures: are measurements of both resting left ventricular ejection fraction and stress-induced myocardial ischemia necessary? <i>J Nucl Cardiol.</i> 2006;13(6):768-778.	Observational-Dx	5,366 patients	To determine whether gated MPS measures of stress perfusion and poststress LV EF predicted which patients would accrue a survival benefit with revascularization versus medical therapy after stress MPS in an observational series of patients who underwent stress MPS.	The percent of myocardium that was ischemic was the most important predictor of revascularization. The overall model (multivariate chi ² = 728, c index = 0.89, P < 10(-5)) was used as a propensity score. Cox proportional hazards analysis, assessing the relationship between MPS results, non-MPS covariates, and cardiac death, revealed that EF was superior to percent ischemic myocardium in the prediction of cardiac death after adjustment for pre-MPS data and the propensity score. However, an interaction between percent ischemic myocardium and revascularization was present such that, irrespective of EF, patients with little or no ischemia had an improved survival rate with medical therapy, whereas with increasing ischemia, progressive improvements in survival rate were noted with revascularization.	3
22. Ali I, Ruddy TD, Almgrahi A, Anstett FG, Wells RG. Half-time SPECT myocardial perfusion imaging with attenuation correction. <i>J Nucl Med.</i> 2009;50(4):554-562.	Observational-Dx	212 patients	To compare half-time (HT) gated myocardial SPECT images processed with ordered-subset expectation maximization with resolution recovery (OSEM-RR) (with and without CT-based attenuation correction [AC]) with full-time (FT) images obtained with a standard clinical protocol and reconstructed with filtered backprojection (FBP) and OSEM (with and without AC).	All measurements resulted in significant correlations (P < 0.01) between the HT and FT images. The only significant difference in mean values was for OSEM-RR plus AC; this method led to an increase in TID by 4% over FT imaging. The concordance in the clinical diagnosis for HT versus FT was 106 to 112 (kappa = 0.88) for no AC and 102 to 106 (kappa = 0.91) for AC, similar to the repeatability of FT versus FT (98/100, kappa = 0.95).	2

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23. Sharir T, Ben-Haim S, Merzon K, Prochorov V, Dickman D, Berman DS. High-speed myocardial perfusion imaging initial clinical comparison with conventional dual detector angler camera imaging. <i>JACC Cardiovasc Imaging</i> . 2008;1(2):156-163.	Observational-Dx	44 patients	To compare myocardial perfusion imaging (MPI) with high-speed single-photon emission computed tomography (SPECT) with conventional SPECT imaging for the evaluation of myocardial perfusion in patients with known or suspected coronary artery disease.	High-speed SPECT SSS and SRS correlated linearly with conventional SPECT respective scores ($r = 0.93$, $p < 0.0001$ for SSS, and $r = 0.93$, $p < 0.0001$ for SRS). Image quality was rated good and higher in 17 (94%) cases for high-speed SPECT and 16 (89%) cases for conventional SPECT. Of the 44 patients studied, 36 (81.8%) and 35 (79.5%) were diagnosed definitely normal or abnormal by conventional and high-speed SPECT, respectively ($p = NS$). Myocardial count rate was significantly higher in high-speed versus conventional SPECT ($384 \times 10(-3) \pm 134 \times 10(-3)$ cpm/min vs. $47 \times 10(-3) \pm 14 \times 10(-3)$ cpm/min, respectively, $p < 0.0001$) for stress and ($962 \times 10(-3) \pm 426 \times 10(-3)$ cpm/min vs. $136 \times 10(-3) \pm 37 \times 10(-3)$ cpm/min, respectively, $p < 0.001$) for rest.	2
24. Schaap J, Kauling RM, Boekholdt SM, et al. Incremental diagnostic accuracy of hybrid SPECT/CT coronary angiography in a population with an intermediate to high pre-test likelihood of coronary artery disease. <i>Eur Heart J Cardiovasc Imaging</i> . 2013;14(7):642-649.	Observational-Dx	98 patients	To evaluate the performance of hybrid SPECT/CCTA vs standalone SPECT and CCTA for the diagnosis of significant CAD in patients with an intermediate to high pre-test likelihood of CAD.	Hybrid SPECT/CCTA was performed prior to conventional coronary angiography including FFR measurements. Hybrid analysis was performed by combined interpretation of SPECT and CCTA images. The sensitivity, specificity, PPV, and NPV were calculated for standalone SPECT, CCTA, and hybrid SPECT/CCTA on per patient level, using an FFR < 0.80 as a reference for significant CAD. Significant CAD was demonstrated in 56 patients (57.9%). Nonconclusive SPECT or CCTA results were found in 32 (32.7%) patients. SPECT had a sensitivity of 93%, specificity 79%, PPV 85%, and NPV 89%. CCTA had a sensitivity of 98%, specificity 62%, PPV 77%, and NPV 96%. Hybrid analysis of SPECT and CCTA improved the overall performance: sensitivity, specificity, PPV, and NPV for the presence of significant CAD to 96%, 95%, 96%, and 95%, respectively.	2

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25. Schaap J, de Groot JA, Nieman K, et al. Hybrid myocardial perfusion SPECT/CT coronary angiography and invasive coronary angiography in patients with stable angina pectoris lead to similar treatment decisions. <i>Heart</i> . 2013;99(3):188-194.	Observational-Dx	107 patients	To evaluate to what extent treatment decisions for patients with stable angina pectoris can be made based on hybrid myocardial perfusion SPECT and CCTA. It has been shown that hybrid SPECT/CCTA has good performance in the diagnosis of significant CAD.	Revascularization (PCI or coronary artery bypass graft) was indicated in 54 (50%) patients based on SPECT and coronary angiography. Percentage agreement of treatment decisions in all patients based on hybrid SPECT/CCTA vs SPECT and coronary angiography on the necessity of revascularization was 92%. Percentage agreement of treatment decisions in patients with matched, unmatched and normal hybrid SPECT/CCTA findings was 95%, 84% and 100%, respectively.	2
26. Danad I, Raijmakers PG, Knaapen P. Diagnosing coronary artery disease with hybrid PET/CT: it takes two to tango. <i>J Nucl Cardiol</i> . 2013;20(5):874-890.	Review/Other-Dx	N/A	To discuss stand-alone CCTA and PET MPI for the diagnosis of CAD, and the clinical application of cardiac hybrid PET/ CCTA in the evaluation for CAD.	Although each of these diagnostic approaches has its own merits and caveats, functional and morphological imaging techniques provide fundamentally different insights into the disease process and should be considered to be complementary rather than overlapping. Hybrid imaging with PET/CT offers the possibility to evaluate both aspects nearly simultaneously, and studies have demonstrated that such a comprehensive assessment results in superior diagnostic accuracy, better prognostication, and helps in guiding clinical patient management.	4

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27. Jaarsma C, Leiner T, Bekkers SC, et al. Diagnostic performance of noninvasive myocardial perfusion imaging using single-photon emission computed tomography, cardiac magnetic resonance, and positron emission tomography imaging for the detection of obstructive coronary artery disease: a meta-analysis. <i>J Am Coll Cardiol.</i> 2012;59(19):1719-1728.	Meta-analysis	166 articles	To determine the diagnostic accuracy of the 3 most commonly used noninvasive MPI modalities, SPECT, CMR, and PET perfusion imaging for the diagnosis of obstructive CAD.	Of the 3,635 citations, 166 articles (n = 17,901) met the inclusion criteria: 114 SPECT, 37 CMR, and 15 PET articles. There were not enough publications on other perfusion techniques such as perfusion ECHO and CT to include these modalities into the study. The patient-based analysis per imaging modality demonstrated a pooled sensitivity of 88% (95% CI: 88% to 89%), 89% (95% CI: 88% to 91%), and 84% (95% CI: 81% to 87%) for SPECT, CMR, and PET, respectively; with a pooled specificity of 61% (95% CI: 59% to 62%), 76% (95% CI: 73% to 78%), and 81% (95% CI: 74% to 87%). This resulted in a pooled diagnostic odds ratio of 15.31 (95% CI: 12.66 to 18.52; I(2) 63.6%), 26.42 (95% CI: 17.69 to 39.47; I(2) 58.3%), and 36.47 (95% CI: 21.48 to 61.92; I(2) 0%). Most of the evaluated test and study characteristics did not affect the ranking of diagnostic performances.	M
28. Bateman TM, Heller GV, McGhie AI, et al. Diagnostic accuracy of rest/stress ECG-gated Rb-82 myocardial perfusion PET: comparison with ECG-gated Tc-99m sestamibi SPECT. <i>J Nucl Cardiol.</i> 2006;13(1):24-33.	Observational-Dx	170 patients	To assess relative image quality, interpretive confidence, and diagnostic accuracy of pharmacologic Tc-99m sestamibi SPECT or Rb-82 PET MPI.	The patients were categorized as having a low likelihood for CAD (27 in each group) or had coronary angiography within 60 days. SPECT scans were acquired on a Cardio-60 system and PET scans on an ECAT ACCEL scanner. Image quality was excellent for 78% and 79% of rest and stress PET scans, respectively, vs 62% and 62% of respective SPECT scans (both $P < .05$). An equal percent of PET and SPECT gated images were rated excellent in quality. Interpretations were definitely normal or abnormal for 96% of PET scans vs 81% of SPECT scans ($P = .001$). Diagnostic accuracy was higher for PET for both stenosis severity thresholds of 70% (89% vs 79%, $P = .03$) and 50% (87% vs 71%, $P = .003$) and was higher in men and women, in obese and nonobese patients, and for correct identification of multivessel CAD.	2

**Chronic Chest Pain—High Probability of Coronary Artery Disease
EVIDENCE TABLE**

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
<p>29. Machac J. Cardiac positron emission tomography imaging. <i>Semin Nucl Med.</i> 2005;35(1):17-36.</p>	<p>Review/Other-Dx</p>	<p>N/A</p>	<p>To review cardiac positron emission tomography imaging.</p>	<p>Although myocardial perfusion PET imaging is an option for all patients requiring stress perfusion imaging, there are identifiable patient groups difficult to image with conventional single-photon emission computed tomography imaging that are particularly likely to benefit from PET imaging, such as obese patients, women, patients with previous nondiagnostic tests, and patients with poor left ventricular function attributable to coronary artery disease considered for revascularization. Myocardial PET perfusion imaging with rubidium-82 is noteworthy for high efficiency, rapid throughput, and in a high-volume setting, low operational costs. PET metabolic viability imaging continues to be a noninvasive standard for diagnosis of viability imaging. Cardiac PET imaging has been shown to be cost-effective. The potential of routine quantification of resting and stress blood flow and coronary flow reserve in response to pharmacologic and cold-pressor stress offers tantalizing possibilities of enhancing the power of PET myocardial perfusion imaging. This can be achieved by providing assurance of stress quality control, in enhancing diagnosis and risk stratification in patients with coronary artery disease, and expanding diagnostic imaging into the realm of detection of early coronary artery disease and endothelial dysfunction subject to risk factor modification. Combined PET and x-ray computed tomography imaging (PET-CT) results in enhanced patient throughput and efficiency. The combination of multislice computed tomography scanners with PET opens possibilities of adding coronary calcium scoring and noninvasive coronary angiography to myocardial perfusion imaging and quantification.</p>	<p>4</p>

**Chronic Chest Pain—High Probability of Coronary Artery Disease
EVIDENCE TABLE**

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
30. Lertsburapa K, Ahlberg AW, Bateman TM, et al. Independent and incremental prognostic value of left ventricular ejection fraction determined by stress gated rubidium 82 PET imaging in patients with known or suspected coronary artery disease. <i>J Nucl Cardiol.</i> 2008;15(6):745-753.	Observational-Dx	1,441 patients	To assess whether EF measurements determined by gated Rb-82 PET MPI provide incremental prognostic value beyond perfusion data in patients with known or suspected CAD.	Annualized mortality rates across SSS groups were 2.4% for SSS of 0 to 3, 4.1% for SSS of 4 to 8, and 6.9% for SSS greater than 8 (P < .001). Similarly, annualized mortality rates were 2.4%, 6.2%, and 9.2% for the group with EF greater than 50%, group with EF of 40% to 49%, and group with EF lower than 40%, respectively (P < .001). On multivariate analysis, the addition of EF to clinical and perfusion variables significantly increased the global chi(2) (73.3 to 107.7, P < .001). Integration of EF with SSS significantly enhanced risk stratification.	3
31. Sampson UK, Dorbala S, Limaye A, Kwong R, Di Carli MF. Diagnostic accuracy of rubidium-82 myocardial perfusion imaging with hybrid positron emission tomography/computed tomography in the detection of coronary artery disease. <i>J Am Coll Cardiol.</i> 2007;49(10):1052-1058.	Observational-Dx	64 patients	To determine the accuracy of rubidium-82 myocardial perfusion positron emission tomography-computed tomography (PET-CT) imaging for detecting obstructive coronary artery disease (CAD).	The mean age of the patients was 62 +/- 15 years, with a body mass index of 31 +/- 8 kg/m2. Chest pain and/or dyspnea were the predominant reasons for evaluation. Stress perfusion defects were detected in 41 of 44 patients with obstructive CAD (sensitivity 93%, 95% confidence interval [CI] 87 to 99). The specificity of PET-CT was 83% (48 of 58, 95% CI 71 to 91), and its overall diagnostic accuracy was 87% (95% CI 79 to 93). All patients with a low likelihood for CAD showed normal scans, for a normalcy rate of 100% (38 of 38, 95% CI 91 to 100). The sensitivity for detecting CAD in patients with single and multivessel (> or =2 vessels) disease was 92% (22 of 24, 95% CI 74 to 99) and 95% (19 of 20, 95% CI 74 to 99), respectively.	3

**Chronic Chest Pain—High Probability of Coronary Artery Disease
EVIDENCE TABLE**

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
32. Di Carli MF, Dorbala S, Curillova Z, et al. Relationship between CT coronary angiography and stress perfusion imaging in patients with suspected ischemic heart disease assessed by integrated PET-CT imaging. <i>J Nucl Cardiol.</i> 2007;14(6):799-809.	Observational-Dx	110 patients	To examine the value of CTA to identify the presence of ischemia, as determined by stress perfusion imaging, using integrated positron emission tomography (PET)-CT imaging.	Increasing degrees of CTA-detected luminal narrowing (<50%, 50%-70%, and >70%) were associated with reduced sensitivity with commensurate improvements in specificity for identifying myocardial ischemia both on a per-vessel basis and on a per-patient basis. Consequently, with increasing degrees of CTA-detected stenosis severity, the positive predictive value increased (14%, 26%, and 53%, respectively, on a per-vessel basis [P < .001] and 29%, 44%, and 77%, respectively, on a per-patient basis [P = .005]), whereas the negative predictive value was unchanged (97%, 97%, and 96%, respectively, on a per-vessel basis [P = not significant (NS)] and 92%, 91%, and 88%, respectively, on a per-patient basis [P = NS]). Receiver operating characteristic analysis revealed no differences between these 3 anatomic criteria (receiver operating characteristic areas of 0.66 +/- 0.07, 0.73 +/- 0.06, and 0.71 +/- 0.07, respectively [P = NS]) for identifying ischemia. Nearly half of significant angiographic stenoses (47%) occurred without evidence of myocardial ischemia, whereas 50% of normal PET studies were associated with some CTA abnormality.	2
33. Namdar M, Hany TF, Koepfli P, et al. Integrated PET/CT for the assessment of coronary artery disease: a feasibility study. <i>J Nucl Med.</i> 2005;46(6):930-935.	Observational-Dx	25 patients	To evaluate if the combination of PET/CT and contrast-enhanced CTA provides comprehensive information of CAD that allows accurate decisions on whether to treat with revascularization or conservatively.	Of the 100 coronary artery segments (left main, left anterior descending, left circumflex, and right in 25 patients), 7 (in 5 patients) were considered impossible to evaluate by CT because of rapid vessel movement but were correctly categorized by PET alone. In the remaining 93 segments, the sensitivity and specificity of PET/CT vs PET plus coronary angiography were 90% and 98%, respectively. PPV and NPV were 82% and 99%, and accuracy was 97%.	3

**Chronic Chest Pain—High Probability of Coronary Artery Disease
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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
34. Fleischmann KE, Hunink MG, Kuntz KM, Douglas PS. Exercise echocardiography or exercise SPECT imaging? A meta-analysis of diagnostic test performance. <i>JAMA</i> . 1998;280(10):913-920.	Meta-analysis	44 articles	To review the contemporary literature and to compare the diagnostic performance of exercise ECHO and exercise SPECT imaging in the diagnosis of CAD.	44 articles met inclusion criteria. In pooled data weighted by the sample size of each study, exercise ECHO had a sensitivity of 85% (95% CI, 83%–87%) with a specificity of 77% (95% CI, 74%–80%). Exercise SPECT yielded a similar sensitivity of 87% (95% CI, 86%–88%) but a lower specificity of 64% (95% CI, 60%–68%). In a summary ROC model comparing exercise ECHO performance to exercise SPECT, exercise ECHO was associated with significantly better discriminatory power (parameter estimate, 1.18; 95% CI, 0.71–1.65), when adjusted for age, publication year, and a setting including known CAD for SPECT studies. In models comparing the discriminatory abilities of exercise ECHO and exercise SPECT vs exercise testing without imaging, both ECHO and SPECT performed significantly better than exercise testing. The incremental improvement in performance was greater for ECHO (3.43; 95% CI, 2.74–4.11) than for SPECT (1.49; 95% CI, 0.91–2.08).	M

Chronic Chest Pain—High Probability of Coronary Artery Disease
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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
35. Quinones MA, Verani MS, Haichin RM, Mahmarian JJ, Suarez J, Zoghbi WA. Exercise echocardiography versus 201Tl single-photon emission computed tomography in evaluation of coronary artery disease. Analysis of 292 patients. <i>Circulation</i> . 1992;85(3):1026-1031.	Observational-Dx	292 patients	To prospectively compare the results of exercise ECHO with those of 201Tl SPECT in a large patient population studied in a laboratory where the 2 techniques have been properly validated.	Exercise ECHO and SPECT were normal in 137 patients and abnormal in 118 (88% agreement). Equal numbers of regional abnormalities were detected by 1 test when missed by the other. The 2 tests had an 82% agreement in detecting the same type of finding within the regions analyzed. SPECT detected more reversible abnormalities than ECHO, whereas ECHO detected more fixed abnormalities than SPECT: Regions with a fixed abnormality by ECHO frequently showed partial reversibility of a perfusion defect by SPECT: Nearly one-third of regions with fixed perfusion defects by SPECT demonstrated normal resting function or reversible abnormalities by ECHO. Sensitivity for CAD by angiography (greater than or equal to 50% diameter stenosis) in 112 patients was similar for the 2 tests, ranging from 58% and 61% (ECHO and SPECT, respectively) for one-vessel disease to 94% for three-vessel disease. The specificities for ECHO and SPECT were 88% and 81%, respectively.	3
36. Schinkel AF, Bax JJ, Geleijnse ML, et al. Noninvasive evaluation of ischaemic heart disease: myocardial perfusion imaging or stress echocardiography? <i>Eur Heart J</i> . 2003;24(9):789-800.	Meta-analysis	17 studies including 1405 patients	To evaluate the value of stress ECHO and MPI in: (1) the detection of CAD, (2) the prognosis of CAD in patients with known or suspected CAD, (3) prediction of functional recovery following acute myocardial infarction and (4) prediction of functional recovery after revascularization in patients with chronic ischemic left ventricle dysfunction.	Pooling of the data showed a slightly higher overall sensitivity for MPI as compared to stress ECHO (84% vs 80%, $P<0.05$). This finding is in line with the ischemic cascade, since perfusion abnormalities (detected by perfusion imaging) proceed systolic dysfunction (detected by stress ECHO). On the other hand, stress ECHO was more specific compared to perfusion imaging (86% vs 77%, $P=0.001$).	M

**Chronic Chest Pain—High Probability of Coronary Artery Disease
EVIDENCE TABLE**

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
37. Smart SC, Bhatia A, Hellman R, et al. Dobutamine-atropine stress echocardiography and dipyridamole sestamibi scintigraphy for the detection of coronary artery disease: limitations and concordance. <i>J Am Coll Cardiol.</i> 2000;36(4):1265-1273.	Observational-Dx	83 patients	To compare dobutamine-atropine stress ECHO and dipyridamole Tc-99m sestamibi SPECT scintigraphy for detecting CAD.	The 183 patients (mean age: 60 +/- 11 years, including 50 women) consisted of 64 patients with no coronary disease and 61 with single-, 40 with two- and 18 with three-vessel coronary disease. Dobutamine-atropine stress ECHO and dipyridamole Tc-99m sestamibi SPECT scintigraphy were similarly sensitive (87%, 104/119 and 80%, 95/119, respectively) for the detection of CAD, but dobutamine-atropine stress ECHO was more specific (91%, 58/64 vs 73%, 47/64, $P<0.01$). Sensitivity was similar for the detection of CAD in patients with single-vessel disease (84%, 51/61 vs 74%, 45/61, respectively) and multivessel disease (91%, 53/58 vs 86%, 50/58, respectively). Multiple wall motion abnormalities and perfusion defects were similarly sensitive for multivessel disease (72%, 42/58 vs 66%, 38/53, respectively), but, again, dobutamine-atropine stress ECHO was more specific than dipyridamole Tc-99m sestamibi SPECT scintigraphy (95%, 119/125 vs 76%, 95/125, respectively, $P<0.01$). Dobutamine-atropine stress ECHO and dipyridamole Tc-99m sestamibi SPECT scintigraphy were moderately concordant for the detection and extent of CAD (Kappa 0.47, $P<0.0001$) but were only fairly (Kappa 0.35, $P<0.001$) concordant for the type of abnormalities (normal, fixed, ischemia or mixed).	3

**Chronic Chest Pain—High Probability of Coronary Artery Disease
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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
38. Marwick T, D'Hondt AM, Baudhuin T, et al. Optimal use of dobutamine stress for the detection and evaluation of coronary artery disease: combination with echocardiography or scintigraphy, or both? <i>J Am Coll Cardiol.</i> 1993;22(1):159-167.	Observational-Dx	217 patients	To examine the efficacy of dobutamine stress 2-D ECHO and perfusion scintigraphy for the detection of CAD in routine practice, to establish the causes of erroneous results and to derive appropriate criteria for the selection of either or both tests.	Significant CAD was found in 142 patients; 102 (72%) were identified by dobutamine ECHO and 108 (76%, $P=NS$) by perfusion imaging. In 75 patients without significant disease, the specificity of dobutamine ECHO was 83% compared with 67% for scintigraphy ($P=0.05$). ECHO sensitivity was lower in patients unable to complete the test because of side effects ($n = 64$) than in the remainder (59% vs 77%, $P=0.02$); this influence was less apparent with scintigraphy (71% vs 78%, $P=NS$). Selective use of scintigraphy in the 31 patients with a negative submaximal stress echocardiogram led to a sensitivity of 80% for this combination. Patients with left ventricular hypertrophy accounted for most of the difference in specificity between ECHO and scintigraphy (94% vs 59%, $P=0.02$). Their respective accuracies were 76% and 73%.	2
39. Picano E, Molinaro S, Pasanisi E. The diagnostic accuracy of pharmacological stress echocardiography for the assessment of coronary artery disease: a meta-analysis. <i>Cardiovasc Ultrasound.</i> 2008;6:30.	Meta-analysis	5 studies; 435 patients	To evaluate the diagnostic accuracy of dobutamine versus dipyridamole stress echocardiography through an evidence-based approach.	The 5 analyzed papers recruited 435 patients, 299 with and 136 without angiographically assessed coronary artery disease (quantitatively assessed stenosis > 50%). Dipyridamole and dobutamine showed similar accuracy (87%, 95% confidence intervals, CI, 83-90, vs. 84%, CI, 80-88, $p = 0.48$), sensitivity (85%, CI 80-89, vs. 86%, CI 78-91, $p = 0.81$) and specificity (89%, CI 82-94 vs. 86%, CI 75-89, $p = 0.15$).	M

**Chronic Chest Pain—High Probability of Coronary Artery Disease
EVIDENCE TABLE**

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
40. Plana JC, Mikati IA, Dokainish H, et al. A randomized cross-over study for evaluation of the effect of image optimization with contrast on the diagnostic accuracy of dobutamine echocardiography in coronary artery disease The OPTIMIZE Trial. <i>JACC Cardiovasc Imaging</i> . 2008;1(2):145-152.	Experimental-Dx	101 patients	To evaluate whether the addition of a contrast agent to dobutamine stress echocardiography (DSE) improves its diagnostic accuracy for coronary artery disease (CAD) and to determine the effect of image quality on the diagnostic impact of contrast agent use in this setting.	A total of 101 patients underwent both DSE studies. Similar hemodynamics were achieved during the 2 stress testing sessions. The use of a contrast agent improved the percentage of segments adequately visualized at baseline (from 72 +/- 24% to 95 +/- 8%) and more so at peak stress (67 +/- 28% to 96 +/- 7%); both p < 0.001. Interpretation of wall motion with high confidence also increased with contrast agent use from 36% to 74% (p < 0.001). Segment visualization with the use of a contrast agent improved in all views, but was more pronounced in the apical views. In unenhanced DSE, 36% of studies were normal, 51% had ischemia, and 8% were uninterpretable-all of which became interpretable with the use of a contrast agent. When compared with angiography (n = 92; 55 patients with CAD), accurate detection of ischemia was higher with contrast-enhanced studies versus nonenhanced studies (p = 0.02). As endocardial visualization and confidence of interpretation decreased in unenhanced studies, a greater impact of the use of a contrast agent on DSE accuracy was observed (p < 0.01).	2
41. Al Sayari S, Kopp S, Bremerich J. Stress cardiac MR imaging: the role of stress functional assessment and perfusion imaging in the evaluation of ischemic heart disease. <i>Radiol Clin North Am</i> . 2015;53(2):355-367.	Review/Other-Dx	N/A	To evaluate the role of CMR stress examination in regard to evaluation of ischemic heart disease including the diagnostic performance and prognostic value.	Stress CMR imaging can provide valuable information for the diagnosis and management of ischemic heart disease. It plays an important role in the initial diagnosis in patients with acute chest pain, in the diagnosis of complications post myocardial infarction, in the assessment of the right ventricle after an acute myocardial infarction, to detect complications due to or after interventions, in prediction of myocardial recovery, to detect inducible ischemia in patients with known ischemic heart disease, in differentiating ischemic from nonischemic dilated cardiomyopathy, and in risk stratification.	4

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
42. al-Saadi N, Gross M, Paetsch I, et al. Dobutamine induced myocardial perfusion reserve index with cardiovascular MR in patients with coronary artery disease. <i>J Cardiovasc Magn Reson</i> . 2002;4(4):471-480.	Observational-Dx	27 patients	To analyze the feasibility of cardiovascular magnetic resonance (CMR) to assess perfusion reserve with dobutamine.	Significant differences were found between ischemic and remote to ischemic segments in patients with single vessel disease (0.90 +/- 0.18 vs. 1.73 +/- 0.32, p < 0.0001). Differences between nonischemic segments in patients without and ischemic segments in patients with coronary artery disease were significant (2.0 +/- 0.39 vs. 0.97 +/- 0.20, p < 0.001). A cut-off value for myocardial perfusion reserve index of 1.22 for the detection of significant coronary artery stenosis yielded a sensitivity, specificity, and diagnostic accuracy of 81, 73, and 77%, respectively.	2
43. Al-Saadi N, Nagel E, Gross M, et al. Noninvasive detection of myocardial ischemia from perfusion reserve based on cardiovascular magnetic resonance. <i>Circulation</i> . 2000;101(12):1379-1383.	Observational-Dx	34 patients	To determine prospectively the diagnostic accuracy of the cutoff value for the detection of significant coronary artery stenosis in patients with suspected coronary artery disease.	A significant difference in myocardial perfusion reserve between ischemic and normal myocardial segments (1.08+/-0.23 and 2.33+/- 0.41; P<0.001) was found that resulted in a cutoff value of 1.5 (mean minus 2 SD of normal segments). In the prospective analysis, sensitivity, specificity, and diagnostic accuracy for the detection of coronary artery stenosis (> or =75%) were 90%, 83%, and 87%, respectively. Interobserver and intraobserver variabilities for the linear fit were low (r=0.96 and 0.99).	3
44. Bettencourt N, Chiribiri A, Schuster A, et al. Direct comparison of cardiac magnetic resonance and multidetector computed tomography stress-rest perfusion imaging for detection of coronary artery disease. <i>J Am Coll Cardiol</i> . 2013;61(10):1099-1107.	Observational-Dx	101 patients	To compare the diagnostic performance of a MDCT integrated protocol including CTA and CTP with CMR-MPI for detection of functionally significant CAD.	On a patient-based model, the MDCT-integrated protocol had a sensitivity, specificity, PPV and NPV of 89%, 83%, 80% and 90%, respectively (global accuracy 85%). These results were closely related with those achieved by CMR-MPI: 89%, 88%, 85% and 91%, respectively (global accuracy 88%). When comparing test accuracies using noninferiority analysis, differences >11% in favor of CMR-MPI can be confidently excluded.	1

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
45. Ishida N, Sakuma H, Motoyasu M, et al. Noninfarcted myocardium: correlation between dynamic first-pass contrast-enhanced myocardial MR imaging and quantitative coronary angiography. <i>Radiology</i> . 2003;229(1):209-216.	Observational-Dx	104 patients	To determine the accuracy of first-pass contrast material-enhanced stress myocardial magnetic resonance (MR) imaging for depiction of myocardial ischemia in patients without myocardial infarction.	The overall sensitivity of MR imaging for depicting at least one coronary artery with significant stenosis was 90% (69 of 77 patients). The sensitivities of MR imaging for depiction of single-, double-, and triple-vessel stenoses were 85% (33 of 39 patients), 96% (22 of 23 patients), and 100% (15 of 15 patients), respectively. The specificity of MR imaging for identification of patients with significant coronary artery stenoses was 85% (23 of 27 patients). The areas under the receiver operating characteristic curve for detection of significant stenosis in individual coronary arteries were 0.888 (observer 1) and 0.911 (observer 2) for MR imaging and 0.707 (observer 1, P <.001) and 0.750 (observer 2, P <.001) for SPECT.	2

**Chronic Chest Pain—High Probability of Coronary Artery Disease
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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
46. Keijer JT, van Rossum AC, van Eenige MJ, et al. Magnetic resonance imaging of regional myocardial perfusion in patients with single-vessel coronary artery disease: quantitative comparison with (201)Thallium-SPECT and coronary angiography. <i>J Magn Reson Imaging</i> . 2000;11(6):607-615.	Observational-Dx	13 patients	To assess the value of first-pass MRI in the clinical evaluation of patients with single-vessel CAD by quantitative comparison of firstpass MRI and 201TI-SPECT.	Defining a perfusion defect as a region with less than 90% of maximum (201)TI intensity, nine patients had a matching perfusion defect, two had no defect on both (201)TI-SPECT or MRI, and one had a defect on (201)TI-SPECT but not on MRI. One patient had a defect on both modalities but with inaccurate localization. Three perfusion parameters were investigated: a) maximum contrast enhancement (MCE); b) slope of the signal intensity versus time curve; and c) inverse mean transit time (1/MTT). The sensitivity and specificity of MCE in the detection of perfusion abnormalities with TI-SPECT as the reference method were 71% and 71%, respectively (slope 77% and 61%, 1/MTT 44% and 70%). Furthermore, correlations were calculated per patient for the entire circumference of the short-axis myocardium. Median correlations were as follows: MCE 0.92, slope 0.91, and 1/MTT 0.40. Mismatches between (201)TI defects and defects on MRI resulted in low mean correlations (MCE 0.45, slope 0.46, and 1/MTT 0.26). There was a trend between severity of perfusion defects on MRI (using MCE) and QCA stenosis area ($r = -0.56$, $P = 0.06$).	3
47. Kwong RY, Schussheim AE, Rekhraj S, et al. Detecting acute coronary syndrome in the emergency department with cardiac magnetic resonance imaging. <i>Circulation</i> . 2003;107(4):531-537.	Observational-Dx	161 patients	To explore whether cardiac MRI at rest can effectively assess possible or probable ACS with a combined examination of regional contractile function, perfusion, and viability.	The sensitivity and specificity, respectively, for detecting acute coronary syndrome were 84% and 85% by MRI, 80% and 61% by an abnormal ECG, 16% and 95% for strict ECG criteria for ischemia (ST depression or T-wave inversion), 40% and 97% for peak troponin-I, and 48% and 85% for a TIMI risk score ≥ 3 . The MRI was more sensitive than strict ECG criteria for ischemia ($P < 0.001$), peak troponin-I ($P < 0.001$), and the TIMI risk score ($P = 0.004$), and MRI was more specific than an abnormal ECG ($P < 0.001$). Multivariate logistic regression analysis showed MRI was the strongest predictor of acute coronary syndrome and added diagnostic value over clinical parameters ($P < 0.001$).	2

* See Last Page for Key

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
48. Nagel E, Klein C, Paetsch I, et al. Magnetic resonance perfusion measurements for the noninvasive detection of coronary artery disease. <i>Circulation</i> . 2003;108(4):432-437.	Observational-Dx	84 patients	To assess the value of myocardial perfusion reserve for the noninvasive detection of CAD in patients with suspected CAD.	ROCs were performed for different criteria to differentiate ischemic and nonischemic segments. Prevalence of CAD was 51%. Best results were achieved when only the 3 inner slices were assessed and a threshold value of 1.1 was used for the second smallest value as a marker for significant CAD. This approach yielded a sensitivity of 88%, specificity of 90%, and accuracy of 89%.	1
49. Paetsch I, Jahnke C, Wahl A, et al. Comparison of dobutamine stress magnetic resonance, adenosine stress magnetic resonance, and adenosine stress magnetic resonance perfusion. <i>Circulation</i> . 2004;110(7):835-842.	Observational-Dx	79 consecutive patients	Prospective study to evaluate the diagnostic value of inducible wall motion abnormalities during dobutamine and adenosine stress MR and adenosine MR perfusion compared with invasive coronary angiography.	Sensitivity and specificity for detection by dobutamine and adenosine stress and adenosine perfusion were 89% and 80%, 40% and 96%, and 91% and 62%, respectively. Dobutamine stress is recommended for current state-of-the-art treatment regimens to detect ischemia in patients with suspected or known CAD but no history of prior MI.	2
50. Schwitter J, DeMarco T, Kneifel S, et al. Magnetic resonance-based assessment of global coronary flow and flow reserve and its relation to left ventricular functional parameters: a comparison with positron emission tomography. <i>Circulation</i> . 2000;101(23):2696-2702.	Experimental-Dx	16 healthy volunteers	To assess the accuracy of CFR determinations by PC-MR technique in comparison with PET.	PET and MR agreed closely for coronary flow reserve (CFR; mean difference, 2.2+/-14.7%; Bland-Altman method). CSF divided by either total left ventricular mass or an estimate of drained myocardium (LVM(drain)) correlated highly with PET flow data (r=0.93 and 0.95, respectively) and with measures of oxygen demand, ie, heart rate, afterload-corrected fiber shortening, and peak systolic stress determined by MR (overall correlation coefficients, 0.81 and 0.87, respectively, multivariate analysis). CSF/LVM(drain) did not differ significantly from PET-derived MBF (difference, 3.6+/-16.6%). In orthotopic heart transplant recipients (n=9), CFR was reduced and blood supply-demand relationships at rest were shifted toward higher flows (P<0.0001).	2

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
51. Schwitter J, Nanz D, Kneifel S, et al. Assessment of myocardial perfusion in coronary artery disease by magnetic resonance: a comparison with positron emission tomography and coronary angiography. <i>Circulation</i> . 2001;103(18):2230-2235.	Observational-Dx	48 patients	To determine the quality of a multislice MR approach with respect to the detection and sizing of compromised myocardium and compare with PET and quantitative coronary angiography.	ROC analysis of subendocardial upslope data revealed a sensitivity and specificity of 91% and 94%, respectively, for the detection of CAD as defined by PET (mean coronary flow reserve minus 2SD of controls) and a sensitivity and specificity of 87% and 85%, respectively, in comparison with quantitative coronary angiography (diameter stenosis \geq 50%). The number of pathological sectors per patient on PET and MR studies correlated linearly (slope, 0.94; $r=0.76$; $P<0.0001$).	3
52. Wilke NM, Jerosch-Herold M, Zenovich A, Stillman AE. Magnetic resonance first-pass myocardial perfusion imaging: clinical validation and future applications. <i>J Magn Reson Imaging</i> . 1999;10(5):676-685.	Review/Other-Dx	N/A	To review the clinical validation and future applications of myocardial magnetic resonance first-pass perfusion imaging.	The spatial resolution (in-plane spatial resolution < 3 mm) is sufficient to differentiate between subendocardial perfusion and subepicardial perfusion. The measurement can be repeated regularly without any adverse effects for the patient. MRI perfusion measurements can be combined with the evaluation of global function and regional wall thickening. Currently, there is no other imaging technique that offers similar advantages. The MRI perfusion measurements can be carried out during baseline conditions and during maximal hyperemia induced with either adenosine or dipyridamole. The ratio of the measured myocardial blood flows provides an estimate of the absolute and relative myocardial perfusion reserve. The perfusion reserve determined with MRFP imaging is a quantitative measure for the assessment of the collateral-dependent myocardial flow.	4

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
53. Greenwood JP, Maredia N, Younger JF, et al. Cardiovascular magnetic resonance and single-photon emission computed tomography for diagnosis of coronary heart disease (CE-MARC): a prospective trial. <i>Lancet</i> . 2012;379(9814):453-460.	Observational-Dx	752 patients	Prospective study to establish the diagnostic accuracy of a multiparametric cardiovascular MR protocol with x-ray coronary angiography as the reference standard and to compare cardiovascular MR with SPECT, in patients with suspected coronary heart disease.	Of the 752 patients, 39% had significant coronary heart disease as identified by x-ray angiography. For multiparametric cardiovascular MR the sensitivity was 86.5% (95% CI, 81.8%–90.1%), specificity 83.4% (79.5%–86.7%), PPV 77.2%, (72.1%–81.6%) and NPV 90.5% (87.1%–93.0%). The sensitivity of SPECT was 66.5% (95% CI, 60.4%–72.1%), specificity 82.6% (78.5%–86.1%), PPV 71.4% (65.3%–76.9%), and NPV 79.1% (74.8%–82.8%). The sensitivity and NPV of cardiovascular MR and SPECT differed significantly ($P<0.0001$ for both) but specificity and PPV did not ($P=0.916$ and $P=0.061$, respectively). Cardiovascular MR had high diagnostic accuracy in coronary heart disease and superiority over SPECT. It should be adopted more widely than at present for the investigation of coronary heart disease.	3
54. Hamon M, Fau G, Nee G, Ehtisham J, Morello R. Meta-analysis of the diagnostic performance of stress perfusion cardiovascular magnetic resonance for detection of coronary artery disease. <i>J Cardiovasc Magn Reson</i> . 2010;12:29.	Meta-analysis	35 studies	To provide a comprehensive and contemporary meta-analysis of its diagnostic accuracy compared with an invasive coronary angiography used as a reference standard.	From the 263 citations identified, 55 relevant original articles were selected. Only 35 fulfilled all of the inclusion criteria, and of these 26 presented data on patient-based analysis. The overall patient-based analysis demonstrated a sensitivity of 89% (95% CI: 88%–91%), and a specificity of 80% (95% CI: 78%–83%). Adenosine stress perfusion CMR had better sensitivity than with dipyridamole (90% (88%–92%) vs 86% (80-90%), $P=0.022$), and a tendency to a better specificity (81% (78-84%) vs 77% (71%–82%), $P=0.065$).	M

**Chronic Chest Pain—High Probability of Coronary Artery Disease
EVIDENCE TABLE**

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
55. de Jong MC, Genders TS, van Geuns RJ, Moelker A, Hunink MG. Diagnostic performance of stress myocardial perfusion imaging for coronary artery disease: a systematic review and meta-analysis. <i>Eur Radiol.</i> 2012;22(9):1881-1895.	Meta-analysis	44 articles	To determine and compare the diagnostic performance of stress MPI for the diagnosis of obstructive CAD, using conventional coronary angiography as the reference standard.	All pooled analyses were based on random effects models. Articles on MRI yielded a total of 2,970 patients from 28 studies; articles on ECHO yielded a sample size of 795 from 10 studies, articles on SPECT yielded 1,323 from 13 studies. For CAD defined as either at least 50%, at least 70% or at least 75% lumen diameter reduction on conventional coronary angiography, the natural logarithms of the diagnostic odds ratio for MRI (3.63; 95 % CI 3.26-4.00) was significantly higher compared to that of SPECT (2.76; 95 % CI 2.28-3.25; $P=0.006$) and that of ECHO (2.83; 95 % CI 2.29-3.37; $P=0.02$). There was no significant difference between the natural logarithms of the diagnostic odds ratio of SPECT and ECHO ($P=0.52$).	M
56. Hundley WG, Hamilton CA, Thomas MS, et al. Utility of fast cine magnetic resonance imaging and display for the detection of myocardial ischemia in patients not well suited for second harmonic stress echocardiography. <i>Circulation.</i> 1999;100(16):1697-1702.	Experimental-Dx	153 patients	To assess the safety and clinical utility of fast cine MRI stress testing for the determination of inducible ischemia in patients not suitable for stress echocardiography.	No patients experienced myocardial infarction, ventricular fibrillation, exacerbation of congestive heart failure, or death. In patients who underwent computer-assisted quantitative coronary angiography, the sensitivity and specificity for detecting a >50% luminal diameter narrowing were 83% and 83%, respectively. In the 103 patients with a negative MRI examination, the cardiovascular occurrence-free survival rate was 97%.	2
57. Nagel E, Lehmkuhl HB, Bocksch W, et al. Noninvasive diagnosis of ischemia-induced wall motion abnormalities with the use of high-dose dobutamine stress MRI: comparison with dobutamine stress echocardiography. <i>Circulation.</i> 1999;99(6):763-770.	Observational-Dx	208 patients	To compare echocardiography and MR for the detection of stress-induced wall motion abnormalities in patients with suspected coronary artery disease.	Eighteen patients could not be examined by DSMR (claustrophobia 11 and adipositas 6) and 18 patients by DSE (poor image quality). Four patients did not reach target heart rate. In 107 patients, coronary artery disease was found. With DSMR, sensitivity was increased from 74.3% to 86.2% and specificity from 69.8% to 85.7% (both $P<0.05$) compared with DSE. Analysis for women yielded similar results.	1

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
58. Hundley WG, Morgan TM, Neagle CM, Hamilton CA, Rerkpattanapipat P, Link KM. Magnetic resonance imaging determination of cardiac prognosis. <i>Circulation</i> . 2002;106(18):2328-2333.	Observational-Dx	279 patients	To determine if the presence of inducible ischemia identified during MRI stress tests could be used to identify those at risk of sustaining a future cardiac event.	279 patients referred (because of poor left ventricular endocardial visualization with echocardiography) for dobutamine/atropine MRI for the detection of inducible ischemia were followed for an average of 20 months. After MRI stress testing, the occurrence of MI, cardiac death, death attributable to any cause, coronary arterial revascularization, and unstable angina or congestive heart failure requiring hospitalization was determined. In a multivariate analysis, the presence of inducible ischemia (HR 3.3, CI 1.1 to 9.7) or an left ventricular ejection fraction <40% (HR 4.2, CI 1.3 to 13.9) was associated with future MI or cardiac death independent of the presence of risk factors for coronary arteriosclerosis.	3
59. Agatston AS, Janowitz WR, Hildner FJ, Zusmer NR, Viamonte M, Jr., Detrano R. Quantification of coronary artery calcium using ultrafast computed tomography. <i>J Am Coll Cardiol</i> . 1990;15(4):827-832.	Observational-Dx	584 patients	To study the ability of ultrafast computed tomography to detect and quantify coronary calcium.	Ultrafast computed tomography was more sensitive than fluoroscopy, detecting coronary calcium in 90% versus 52% of patients. There were significant differences (p less than 0.0001) in mean total calcium scores for those with versus those without clinical coronary artery disease by decade: 5 versus 132, age 30 to 39 years; 27 versus 291, age 40 to 49 years; 83 versus 462, age 50 to 59 years; and 187 versus 786, age 60 to 69 years. Sensitivity, specificity and predictive values for clinical coronary artery disease were calculated for several total calcium scores in each decade. For age groups 40 to 49 and 50 to 59 years, a total score of 50 resulted in a sensitivity of 71% and 74% and a specificity of 91% and 70%, respectively. For age group 60 to 69 years, a total score of 300 gave a sensitivity of 74% and a specificity of 81%. The negative predictive value of a 0 score was 98%, 94% and 100% for age groups 40 to 49, 50 to 59 and 60 to 69 years, respectively.	3

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
60. Agatston AS, Janowitz WR, Kaplan G, Gasso J, Hildner F, Viamonte M, Jr. Ultrafast computed tomography-detected coronary calcium reflects the angiographic extent of coronary arterial atherosclerosis. <i>Am J Cardiol.</i> 1994;74(12):1272-1274.	Observational-Dx	100 patients	To study the correlation between quantitative measures of coronary calcium by ultrafast CT and the extent of atherosclerosis documented by coronary angiography.	This study demonstrates the potential of ultrafast CT quantification of coronary calcium to reflect the extent of atherosclerosis measured by coronary angiography. The findings are concordant with pathology studies that have also shown a close relation between the extent of coronary calcium and the extent of atherosclerosis. ⁶ The usefulness of this technique in finding a population of asymptomatic subjects in whom aggressive risk factor modification would be cost-effective should be explored.	3
61. Breen JF, Sheedy PF, 2nd, Schwartz RS, et al. Coronary artery calcification detected with ultrafast CT as an indication of coronary artery disease. <i>Radiology.</i> 1992;185(2):435-439.	Observational-Dx	100 patients	To assess (a) the relationship between the quantity of coronary calcification at ultrafast CT and the severity of occlusive coronary artery disease at angiography and (b) the performance of ultrafast CT as a potential screening examination for detection of atherosclerotic coronary disease in patients less than 60 years of age.	All patients with clinically significant disease at angiography (defined as at least one stenosis with a diameter narrowing of at least 50%) had some coronary artery calcification present at ultrafast CT (100% sensitivity in this population). The absence of calcification at ultrafast CT had a 100% negative predictive value for clinically significant coronary artery disease. Specificity and positive predictive value were 47% and 62%, respectively. Sensitivity and specificity of ultrafast CT in the detection of patients with angiographically detectable disease were 94% and 72%, respectively.	2
62. Carr JJ, Crouse JR, 3rd, Goff DC, Jr., D'Agostino RB, Jr., Peterson NP, Burke GL. Evaluation of subsecond gated helical CT for quantification of coronary artery calcium and comparison with electron beam CT. <i>AJR Am J Roentgenol.</i> 2000;174(4):915-921.	Observational-Dx	36 patients	To compare calcium scores obtained with retrospectively gated helical CT and the current standard, electron beam CT.	Correlation coefficients ranged from 0.97 to 0.98 (Pearson's product moment) and from 0.95 to 0.96 (Spearman's rank order), depending on the coronary calcium scoring method used. Agreement in the classification of participants as "healthy" or "diseased" at threshold total calcium scores of 10, 100, 160, 200, 400, and 680 was, respectively, 94%, 97%, 89%, 92%, 94%, and 100% using the conventional electron beam CT scoring method and an equivalent method with helical CT.	3

**Chronic Chest Pain—High Probability of Coronary Artery Disease
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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
63. de Agustin JA, Marcos-Alberca P, Fernandez-Golfin C, et al. Should computed tomography coronary angiography be aborted when the calcium score exceeds a certain threshold in patients with chest pain? <i>Int J Cardiol.</i> 2013;167(5):2013-2017.	Observational-Dx	294 patients	To discover whether specific “cutpoints” regarding coronary artery calcium score could be determined to predict severe coronary stenoses assessed by CCTA, thus identifying patients amenable to an invasive diagnostic approach.	Severe coronary stenoses were noted in 75/294 (25.1%) patients on CCTA. A very high prevalence of severe coronary stenoses was found in patients with calcium score ≥ 400 (87.0%). The calcium score had AUC 0.86 to predict severe coronary stenoses on CCTA. The best discriminant cut-off point was calcium score ≥ 400 (sensitivity of 55.3%, specificity of 93.5%, PPV of 85.8%, NPV of 84.0%). Multivariable logistic regression analysis controlling for traditional risk factors showed calcium score ≥ 400 remained an independent predictor of severe coronary stenoses on CCTA (odds ratio 14.553, 95% CI, 4.043 to 52.384, $P < 0.001$).	3
64. Detrano RC, Anderson M, Nelson J, et al. Coronary calcium measurements: effect of CT scanner type and calcium measure on rescan reproducibility--MESA study. <i>Radiology.</i> 2005;236(2):477-484.	Observational-Dx	6,814 patients	To evaluate the effect of scanner type and calcium measure on the reproducibility of calcium measurements.	Concordance for presence of calcium between duplicate scans was high and similar for both electron-beam and multi-detector row CT (96%, kappa = 0.92). Mean absolute difference between calcium scores for the two scans was 15.8 for electron-beam and 16.9 for multi-detector row CT scanners ($P = .06$). Mean relative differences were 20.1 for Agatston score, 18.3 for calcium volume, and 18.3 for interpolated volume score ($P < .01$). Reproducibility was lower for scans with versus those without image misregistrations or motion artifacts ($P < .01$ for both).	2
65. Fallavollita JA, Brody AS, Bunnell IL, Kumar K, Canty JM, Jr. Fast computed tomography detection of coronary calcification in the diagnosis of coronary artery disease. Comparison with angiography in patients < 50 years old. <i>Circulation.</i> 1994;89(1):285-290.	Observational-Dx	106 patients under 50 years of age	To compare the results of calcification detected by fast CT with those by coronary angiography in patients <50 years of age.	Calcification detected by fast CT had an 85% sensitivity to predict patients with significant coronary artery disease ($> \text{ or } = 50\%$ diameter stenosis), with a specificity of 45%. Although the sensitivity to detect multivessel disease was 94%, the sensitivity to detect single-vessel disease was 75%. Changing the threshold for defining a positive fast CT scan from 4 to 2 contiguous voxels produced a small improvement in sensitivity, to 88%, but reduced specificity to 36%.	2

**Chronic Chest Pain—High Probability of Coronary Artery Disease
EVIDENCE TABLE**

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
66. Nasir K, Clouse M. Role of nonenhanced multidetector CT coronary artery calcium testing in asymptomatic and symptomatic individuals. <i>Radiology</i> . 2012;264(3):637-649.	Review/Other-Dx	N/A	To examine in detail the methods, value, and potential role of noncontrast-enhanced, or noncontrast, CT assessment of CAD for risk stratification in asymptomatic and symptomatic individuals.	No results stated in abstract.	4
67. Stanford W, Thompson BH, Burns TL, Heery SD, Burr MC. Coronary artery calcium quantification at multi-detector row helical CT versus electron-beam CT. <i>Radiology</i> . 2004;230(2):397-402.	Observational-Dx	78 asymptomatic subjects	To compare coronary artery calcium scores from a multi-detector row helical computed tomographic (CT) scanner with those from an electron-beam CT scanner, with emphasis on subjects with calcium scores less than 400.	Electron-beam CT calcium scores were higher than multi-detector row CT scores. Linear association between calcium scores obtained from paired scans was significant ($r = 0.96-0.99$, $P < .001$). Mean percent absolute differences were 67.9% and 65.0% for volume and Agatston scores, respectively (48.6% and 46.3% for corresponding natural log-transformed scores). In subjects with a score of 11 or greater, mean percent absolute differences between electron-beam CT and multi-detector row CT scores ranged from 15% to 30% (<10% for natural log-transformed calcium scores). With a 20% equivalence limit, calcium scores from the two scanners were statistically equivalent ($P < .05$). Score grouping would have been subject to change in 12 (11 increased and one decreased; six with scores of 11 or greater), and possible risk management decisions would have been subject to change in eight (16%) of 51 subjects who underwent electron-beam CT versus multi-detector row CT scanning.	3

**Chronic Chest Pain—High Probability of Coronary Artery Disease
EVIDENCE TABLE**

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
68. Wong ND, Vo A, Abrahamson D, Tobis JM, Eisenberg H, Detrano RC. Detection of coronary artery calcium by ultrafast computed tomography and its relation to clinical evidence of coronary artery disease. <i>Am J Cardiol.</i> 1994;73(4):223-227.	Observational-Dx	1,218 patients	To evaluate the sensitivity and predictive value of ultrafast CT coronary artery scanning in relation to reported history of CAD, including the impact of age and preexisting risk factors on the ability of this test to identify CAD.	Total score was 3 to 6 times greater ($p < 0.01$) and the probability of coronary artery calcium 30 to 40% greater ($p < 0.01$) in patients with a reported history of myocardial infarction, positive angiography, bypass surgery or angioplasty. From score cutoffs ranging from 1 to 500 for defining calcium, a negative test was accurate 93 to 98% of the time in ruling out CAD, whereas specificity increased from 43 to 93%; however, sensitivity decreased from 92 to 42%. A score cutoff of 50 showed modest sensitivity (78%) and specificity (71%); however, the predictive value for CAD from a positive test remained low ($< \text{or} = 40\%$), regardless of score cutoff. From multiple logistic regression, total score was also an independent indicator of CAD after considering any effects due to age, sex and other CAD risk factors.	3
69. Yerramasu A, Lahiri A, Venuraju S, et al. Diagnostic role of coronary calcium scoring in the rapid access chest pain clinic: prospective evaluation of NICE guidance. <i>Eur Heart J Cardiovasc Imaging.</i> 2014;15(8):886-892.	Observational-Dx	300 patients	To prospectively examine the value of coronary artery calcium imaging by unenhanced CT, as an initial diagnostic test for patients with stable chest pain symptoms but a low likelihood of CAD, in a rapid access chest pain clinic.	The mean patient age was 60.6 (SD 9.6) years and 48% were males. Obstructive CAD was found in 56 (19%) patients, of whom 42 (14%) underwent revascularization. Coronary artery calcium was zero in 131 (44%) patients, of whom 2 (1.5%) had obstructive CAD and 1 (0.8%) underwent revascularization. The sensitivity, specificity, NPV, and PPV of coronary artery calcium ≥ 1 for detection of obstructive CAD were 96%, 53%, 32%, and 98%, respectively. None of the 57 patients with low pre-test probability of CAD and zero coronary artery calcium had obstructive CAD or suffered a cardiovascular event during the follow-up.	3

**Chronic Chest Pain—High Probability of Coronary Artery Disease
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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
70. Shaw LJ, Raggi P, Schisterman E, Berman DS, Callister TQ. Prognostic value of cardiac risk factors and coronary artery calcium screening for all-cause mortality. <i>Radiology</i> . 2003;228(3):826-833.	Observational-Dx	10,377 asymptomatic patients	To develop risk-adjusted multivariable models that included risk factors and coronary calcium scores determined with EBCT in asymptomatic patients for the prediction of all-cause mortality.	During a mean follow-up of 5.0 years +/- 0.0086 (standard error of the mean), the death rate was 2.4%. In a risk-adjusted model (model chi2 = 388.2, P<.001), coronary calcium was an independent predictor of mortality (P<.001). Risk-adjusted RR values for coronary calcium were 1.64, 1.74, 2.54, and 4.03 for scores of 11-100, 101-400, 401-1,000, and greater than 1,000, respectively (P<.001 for all values), as compared with that for a score of 10 or less. 5-year risk-adjusted survival was 99.0% for a calcium score of 10 or less and 95.0% for a score of greater than 1,000 (P<.001). With a ROC curve, the concordance index increased from 0.72 for cardiac risk factors alone to 0.78 (P<.001) when the calcium score was added to a multivariable model for prediction of death.	3
71. Kim YJ, Hur J, Lee HJ, et al. Meaning of zero coronary calcium score in symptomatic patients referred for coronary computed tomographic angiography. <i>Eur Heart J Cardiovasc Imaging</i> . 2012;13(9):776-785.	Observational-Dx	2088 patients. Of these a coronary calcium score of zero was detected in 1114 patients	To determine the meaning of a coronary calcium score of zero in a large sample of symptomatic patients referred for CCTA.	A coronary calcium score of zero was detected in 1114 patients (471 men and 643 women). Of these 1114 patients, obstructive CAD was found in a total of 48 patients (4.3%); 35 men (7.4%) and 13 women (2.0%). Among the zero coronary calcium score patients with obstructive CAD, men had a higher prevalence of both premature CAD (49% vs 0%) and multivessel disease (20% vs 8%) than women. During the follow-up period (1033 +/- 136 days), early revascularization was done in 25 patients (2.2%, 18 men and 7 women) and there were 14 major adverse cardiac events (1.3%, 8 men and 7 women) among the zero coronary calcium score patients. CAD severity was a strong prognostic indicator in the zero coronary calcium score patients.	2

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
72. Mollet NR, Cademartiri F, van Mieghem CA, et al. High-resolution spiral computed tomography coronary angiography in patients referred for diagnostic conventional coronary angiography. <i>Circulation</i> . 2005;112(15):2318-2323.	Observational-Dx	52 patients	To report the diagnostic performance of 64-slice CT coronary angiography in 52 patients with atypical chest pain, stable or unstable angina, or non-ST-segment elevation myocardial infarction referred for diagnostic invasive coronary angiography to assess the extent and severity of coronary stenoses in the clinically relevant coronary tree.	Invasive coronary angiography demonstrated the absence of significant disease in 25% (13 of 52), single-vessel disease in 31% (16 of 52), and multivessel disease in 45% (23 of 52) of patients. One unsuccessful CT scan was classified as inconclusive. Ninety-four significant stenoses were present in the remaining 51 patients. Sensitivity, specificity, and positive and negative predictive values of CT for detecting significant stenoses on a segment-by-segment analysis were 99% (93 of 94; 95% CI, 94 to 99), 95% (601 of 631; 95% CI, 93 to 96), 76% (93 of 123; 95% CI, 67 to 89), and 99% (601 of 602; 95% CI, 99 to 100), respectively.	1
73. Pugliese F, Mollet NR, Runza G, et al. Diagnostic accuracy of non-invasive 64-slice CT coronary angiography in patients with stable angina pectoris. <i>Eur Radiol</i> . 2006;16(3):575-582.	Observational-Dx	35 patients	To evaluate the diagnostic performance of 64-slice CT coronary angiography in the detection of significant stenoses (defined as > or = 50% luminal diameter reduction) versus invasive quantitative coronary angiography (QCA).	The sensitivity, specificity and the positive and negative predictive values of 64-slice CT were 99%, 96%, 78% and 99%, respectively, on a per-segment basis. The values obtained on a per-patient basis were 100%, 90%, 96% and 100%, respectively.	1
74. Ropers D, Rixe J, Anders K, et al. Usefulness of multidetector row spiral computed tomography with 64- x 0.6-mm collimation and 330-ms rotation for the noninvasive detection of significant coronary artery stenoses. <i>Am J Cardiol</i> . 2006;97(3):343-348.	Observational-Dx	84 patients	To determine the accuracy of noninvasive coronary angiography using a multidetector computed tomographic scanner with 64- x 0.6-mm collimation and 330-ms gantry rotation.	After exclusion of unevaluable coronary segments (4%), multidetector computed tomography demonstrated a sensitivity of 93%, a specificity of 97%, and a negative predictive value of 100% in a per-segment analysis. In a per-artery analysis, 15 of 336 arteries (4%) were unevaluable. Sensitivity and specificity in evaluable arteries were 95% and 93%, respectively. In a per-patient analysis (81 of 84 patients included), sensitivity and specificity were 96% and 91%, respectively.	2

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
75. Schlattmann P, Schuetz GM, Dewey M. Influence of coronary artery disease prevalence on predictive values of coronary CT angiography: a meta-regression analysis. <i>Eur Radiol.</i> 2011;21(9):1904-1913.	Meta-analysis	89 studies; 7,516 patients	To evaluate the impact of coronary artery disease (CAD) prevalence on the predictive values of coronary CT angiography.	The summary negative and positive predictive values of coronary CT angiography were 93.7% (95% confidence interval [CI] 92.8-94.5%) and 87.5% (95% CI, 86.5-88.5%), respectively. With 95% confidence, negative and positive predictive values higher than 90% and 70% were available with CT for a CAD prevalence of 18-63%. CT systems with >16 detector rows met these requirements for the positive (P < 0.01) and negative (P < 0.05) predictive values in a significantly broader range than systems with <=16 detector rows.	M
76. Abdulla J, Abildstrom SZ, Gotzsche O, Christensen E, Kober L, Torp-Pedersen C. 64-multislice detector computed tomography coronary angiography as potential alternative to conventional coronary angiography: a systematic review and meta-analysis. <i>Eur Heart J.</i> 2007;28(24):3042-3050.	Meta-analysis	27 studies; 1,740 patients	To evaluate the diagnostic accuracy of 64-slice multi-detector computed tomography coronary angiography (64-SCTA) compared with the standard reference conventional coronary angiography (CCA).	Based on a systematic search, 27 studies including 1740 patients were eligible for meta-analyses. Nineteen studies examined native coronary arteries (n = 1,251), four studies examined coronary artery by-pass grafts (CABG) (n = 271), and five studies examined coronary stents (n = 270). Overall 18 920 segments were assessable and 810 (4%) were unassessable. The prevalence of native coronary artery stenosis in per-segment (19 studies) and per-patients (13 studies) populations were 19 and 57.5% respectively. Accuracy tests with 95% confidence intervals comparing 64-SCTA vs. CCA showed that sensitivity, specificity, positive predictive and negative predictive values for native coronary arteries were 86(85-87), 96(95.5-96.5), 83, and 96.5% by per-segment analysis; 97.5(96-99), 91(87.5-94), 93, and 96.5% by per-patient analysis; 98.5(96-99.5), 96(93.5-97.5), 92 and 99% for CABGs; 80(70-88.5), 95(92-97), 80, and 95% for stent restenosis; and 87(86.5-88), 96(95.5-96.5), 83.5, and 97% by overall per-segment analysis.	M

**Chronic Chest Pain—High Probability of Coronary Artery Disease
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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
77. Abdulla J, Pedersen KS, Budoff M, Kofoed KF. Influence of coronary calcification on the diagnostic accuracy of 64-slice computed tomography coronary angiography: a systematic review and meta-analysis. <i>Int J Cardiovasc Imaging</i> . 2012;28(4):943-953.	Meta-analysis	19 studies; 1,634 patients	To determine via meta-analysis the diagnostic accuracy of 64-slice computed tomography coronary angiography (CTA) for assessment of significant obstructive coronary artery stenosis at different coronary artery calcium score (CACS) levels.	The per-patient prevalence of coronary artery disease was 48% versus 68%, respectively. Subgroups were stratified by different CACS thresholds ranging from 100 to 400. Meta-analyses of per-patient data comparing overall low versus high CACS subgroups resulted in a sensitivity of 97.5 (95.5-99)% versus 97 (94.5-98.5)%, specificity of 85 (82-88)% versus 66.5 (58-74.5)%, diagnostic odds ratio of 153 (81-290) versus 40 (20-83), positive predictive value of 85 (82-87)% versus 86 (84-88)%, negative predictive value of 97.5 (95-99)% versus 91 (88-94)% and overall accuracy of 91% versus 89% with 95% confidence interval, respectively. The drop in specificity was significant (P = 0.035), while the sensitivity and overall accuracy were insignificantly changed (P > 0.05). Meta-analyses of independent subgroups at CACS levels <=10 and <=100 demonstrated high specificities of 90 (94-100)% and 88.5 (81-91.5)%, whereas at CACS levels >=400 the specificity declined significantly to 42 (28-56)% but with consistently retained high sensitivity of 97.5 (94-99)%. The specificity of CTA decreases with increasing CACS, while the sensitivity remains high independent of that.	M
78. Carrascosa PM, Deviggiano A, Capunay C, et al. Incremental value of myocardial perfusion over coronary angiography by spectral computed tomography in patients with intermediate to high likelihood of coronary artery disease. <i>Eur J Radiol</i> . 2015;84(4):637-642.	Observational-Dx	25 patients	To explore the diagnostic performance of DECT for the evaluation of myocardial perfusion in patients with intermediate to high likelihood of CAD.	A total of 425 left ventricular segments were evaluated by DECT, showing a reliable accuracy for the detection of reversible perfusion defects [AUC 0.84 (0.80–0.87)]. Furthermore, adding stress myocardial perfusion provided a significant incremental value over anatomical evaluation alone by CCTA [AUC 0.70 (0.65–0.74), P=0.003].	2

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
79. Budoff MJ, Dowe D, Jollis JG, et al. Diagnostic performance of 64-multidetector row coronary computed tomographic angiography for evaluation of coronary artery stenosis in individuals without known coronary artery disease: results from the prospective multicenter ACCURACY (Assessment by Coronary Computed Tomographic Angiography of Individuals Undergoing Invasive Coronary Angiography) trial. <i>J Am Coll Cardiol.</i> 2008;52(21):1724-1732.	Experimental-Dx	230 patients	To evaluate the diagnostic accuracy of electrocardiographically gated 64-multidetector row CCTA in individuals without known CAD.	On a patient-based model, the sensitivity, specificity, and NPV and NPVs to detect $\geq 50\%$ or $\geq 70\%$ stenosis were 95%, 83%, 64%, and 99%, respectively, and 94%, 83%, 48%, 99%, respectively. No differences in sensitivity and specificity were noted for nonobese compared with obese subjects or for heart rates ≤ 65 beats/min compared with > 65 beats/min, whereas calcium scores > 400 reduced specificity significantly.	1
80. Arbab-Zadeh A, Miller JM, Rochitte CE, et al. Diagnostic accuracy of computed tomography coronary angiography according to pre-test probability of coronary artery disease and severity of coronary arterial calcification. The CORE-64 (Coronary Artery Evaluation Using 64-Row Multidetector Computed Tomography Angiography) International Multicenter Study. <i>J Am Coll Cardiol.</i> 2012;59(4):379-387.	Observational-Dx	371 patients	To assess the impact of patient population characteristics on accuracy by computed tomography angiography (CTA) to detect obstructive coronary artery disease (CAD).	Analysis of patient-based quantitative CTA accuracy revealed an AUC of 0.93 (95% confidence interval [CI]: 0.90 to 0.95). The AUC remained 0.93 (95% CI: 0.90 to 0.96) after excluding patients with known CAD but decreased to 0.81 (95% CI: 0.71 to 0.89) in patients with calcium score ≥ 600 ($p = 0.077$). While AUCs were similar (0.93, 0.92, and 0.93, respectively) for patients with intermediate, high pre-test probability for CAD, and known CAD, negative predictive values were different: 0.90, 0.83, and 0.50, respectively. Negative predictive values decreased from 0.93 to 0.75 for patients with calcium score < 100 or ≥ 100 , respectively ($p = 0.053$).	2
81. Husmann L, Schepis T, Scheffel H, et al. Comparison of diagnostic accuracy of 64-slice computed tomography coronary angiography in patients with low, intermediate, and high cardiovascular risk. <i>Acad Radiol.</i> 2008;15(4):452-461.	Observational-Dx	88 patients	To compare the diagnostic accuracy of 64-slice CCTA in groups of patients with low, intermediate, and high risk for CAD events.	Per-patient sensitivity, specificity, NPV, and PPV were 90.0%, 79.2%, 95.0%, and 64.3%, respectively, with low ($n = 34$), 87.5%, 92.3%, 85.7%, and 93.3%, respectively, with intermediate ($n = 29$), and 100%, 75.0%, 100%, and 89.5%, respectively, with high risk ($n = 25$), with a trend toward higher PPV ($P = .07$). Per-segment NPV was lower with high pretest probability ($P < .01$). Mean calcium-score units were 90, 220, and 312 ($P = .23$), and the prevalence of CAD was 29.4%, 55.2%, and 68.0% ($P < .01$) with low, intermediate, and high risk.	2

**Chronic Chest Pain—High Probability of Coronary Artery Disease
EVIDENCE TABLE**

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
82. Meijboom WB, van Mieghem CA, Mollet NR, et al. 64-slice computed tomography coronary angiography in patients with high, intermediate, or low pretest probability of significant coronary artery disease. <i>J Am Coll Cardiol</i> . 2007;50(15):1469-1475.	Observational-Dx	254 patients	To assess the usefulness of 64-slice CCTA to detect or rule out CAD in patients with various estimated pretest probabilities of CAD.	The estimated pretest probability of CAD in the high (n = 105), intermediate (n = 83), and low (n = 66) groups was 87%, 53%, and 13%, respectively. The diagnostic performance of the CT scan was different in the 3 subgroups. The estimated post-test probability of the presence of significant CAD after a negative CT scan was 17%, 0%, and 0% and after a positive CT scan was 96%, 88%, and 68%, respectively.	3
83. Magalhaes TA, Kishi S, George RT, et al. Combined coronary angiography and myocardial perfusion by computed tomography in the identification of flow-limiting stenosis - The CORE320 study: An integrated analysis of CT coronary angiography and myocardial perfusion. <i>J Cardiovasc Comput Tomogr</i> . 2015;9(5):438-445.	Observational-Dx	381 patients	To investigate the accuracy of a combined CCTA and myocardial CTP comprehensive protocol compared to CCTA alone, using a combination of invasive coronary angiography and SPECT as reference.	Mean patient age was 62 +/- 6 years (66% male), 27% with prior history of myocardial infarction. In a per-patient analysis, sensitivity for CTA alone was 93%, specificity was 54%, PPV was 55%, NPV was 93%, and overall accuracy was 69%. After combining CTA and CTP, sensitivity was 78%, specificity was 73%, NPV was 64%, PPV was 0.85%, and overall accuracy was 75%. In a per-vessel analysis, overall accuracy of CTA alone was 73% compared to 79% for the combination of CTA and CTP ($P < .0001$ for difference).	2
84. Pontone G, Andreini D, Baggiano A, et al. Functional relevance of coronary artery disease by cardiac magnetic resonance and cardiac computed tomography: myocardial perfusion and fractional flow reserve. <i>Biomed Res Int</i> . 2015;2015:297696.	Review/Other-Dx	N/A	To evaluate the technical aspects and clinical experience of stress-CMR and CCT in the evaluation of functional relevance of CAD discussing the strength and weakness of each approach.	No results stated in abstract.	4

Chronic Chest Pain—High Probability of Coronary Artery Disease
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
85. Varga-Szemes A, Meinel FG, De Cecco CN, Fuller SR, Bayer RR, 2nd, Schoepf UJ. CT myocardial perfusion imaging. <i>AJR Am J Roentgenol.</i> 2015;204(3):487-497.	Review/Other-Tx	N/A	To provide a systematic overview of the presently available approaches for the assessment of CT MPI, including diagnostic accuracy and limitations	A growing body of clinical evidence shows that combined CCTA and CT MPI enables the morphologic and functional assessment of CAD with high accuracy in a single technique. CT MPI is most likely to be used as an add-on to CCTA to increase the specificity for hemodynamically relevant lesions, particularly in the setting of a stenosis of intermediate severity. Most existing studies on CT MPI were performed in a limited number of patients to test clinical feasibility and diagnostic accuracy. Larger studies are slowly emerging, but much more evidence is needed to better define the potential role of CT MPI for clinical decision making in patients with ischemic heart disease.	4
86. Osawa K, Miyoshi T, Koyama Y, et al. Additional diagnostic value of first-pass myocardial perfusion imaging without stress when combined with 64-row detector coronary CT angiography in patients with coronary artery disease. <i>Heart.</i> 2014;100(13):1008-1015.	Observational-Dx	145 patients	To evaluate the usefulness of first-pass CT-MPI in combination with CCTA for diagnosing CAD.	First-pass CT-MPI in combination with CCTA significantly improved diagnostic performance compared with CCTA alone. With per-vessel analysis, the sensitivity, specificity, PPV and NPV increased from 81% to 85%, 87% to 94%, 63% to 79% and 95% to 96%, respectively. AUC for detecting CAD also increased from 0.84 to 0.89 ($P=0.02$). First-pass CT-MPI was particularly useful for assessing segments that could not be directly evaluated due to severe calcification and motion artefacts.	3

**Chronic Chest Pain—High Probability of Coronary Artery Disease
EVIDENCE TABLE**

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
87. Rochitte CE, George RT, Chen MY, et al. Computed tomography angiography and perfusion to assess coronary artery stenosis causing perfusion defects by single photon emission computed tomography: the CORE320 study. <i>Eur Heart J</i> . 2014;35(17):1120-1130.	Experimental-Dx	381 patients	To evaluate the diagnostic power of integrating the results of CTA and CTP to identify CAD defined as a flow limiting coronary artery stenosis causing a perfusion defect by SPECT.	The prevalence of obstructive CAD defined by combined invasive coronary angiography-SPECT/MPI and invasive coronary angiography alone was 38% and 59%, respectively. The patient-based diagnostic accuracy defined by the AUC of integrated CTA-CTP for detecting or excluding flow-limiting CAD was 0.87 [95% CI: 0.84–0.91]. In patients without prior myocardial infarction, the AUC was 0.90 (95% CI: 0.87–0.94) and in patients without prior CAD the AUC for combined CTA-CTP was 0.93 (95% CI: 0.89–0.97). For the combination of a CTA stenosis \geq 50% stenosis and a CTP perfusion deficit, the sensitivity, specificity, PPV, and NPV (95% CI) were 80% (72–86), 74% (68–80), 65% (58–72), and 86% (80–90), respectively. For flow-limiting disease defined by invasive coronary angiography-SPECT/MPI, the accuracy of CTA was significantly increased by the addition of CTP at both the patient and vessel levels.	1
88. George RT, Arbab-Zadeh A, Miller JM, et al. Adenosine stress 64- and 256-row detector computed tomography angiography and perfusion imaging: a pilot study evaluating the transmural extent of perfusion abnormalities to predict atherosclerosis causing myocardial ischemia. <i>Circ Cardiovasc Imaging</i> . 2009;2(3):174-182.	Observational-Dx	40 patients	To test whether adenosine stress CTP, when added to CTA, can predict perfusion abnormalities caused by obstructive atherosclerosis.	CTA and quantitative coronary angiography were evaluated for stenoses \geq 50%, and SPECT-MPI was evaluated for fixed and reversible perfusion deficits using a 17-segment model. CTP images were analyzed for the transmural differences in perfusion using the transmural perfusion ratio (subendocardial attenuation density/subepicardial attenuation density). The sensitivity, specificity, PPV, and NPV for the combination of CTA and CTP to detect obstructive atherosclerosis causing perfusion abnormalities using the combination of quantitative coronary angiography and SPECT as the gold standard was 86%, 92%, 92%, and 85% in the per-patient analysis and 79%, 91%, 75%, and 92% in the per vessel/territory analysis, respectively.	2

**Chronic Chest Pain—High Probability of Coronary Artery Disease
EVIDENCE TABLE**

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
89. George RT, Arbab-Zadeh A, Miller JM, et al. Computed tomography myocardial perfusion imaging with 320-row detector computed tomography accurately detects myocardial ischemia in patients with obstructive coronary artery disease. <i>Circ Cardiovasc Imaging</i> . 2012;5(3):333-340.	Observational-Dx	50 patients	To assess the accuracy of 320-row CTP to detect atherosclerosis causing myocardial ischemia.	CTA alone was a limited predictor of myocardial ischemia compared with SPECT, with a sensitivity, specificity, PPV and NPV of 56%, 75%, 56%, and 75%, and the AUC was 0.65 (95% CI, 0.51–0.78, $P=0.07$). CTP was a better predictor of myocardial ischemia, with a sensitivity, specificity, PPV, and NPV of 72%, 91%, 81%, and 85%, with an AUC of 0.81 (95% CI, 0.68–0.91, $P<0.001$), and was an excellent predictor of myocardial ischemia on SPECT-MPI in the presence of stenosis ($\geq 50\%$ on CTA), with a sensitivity, specificity, PPV, and NPV of 100%, 81%, 50%, and 100%, with an AUC of 0.92 (95% CI, 0.80–0.97, $P<0.001$). The radiation dose for the comprehensive cardiac CT protocol and SPECT were 13.8 \pm 2.9 and 13.1 \pm 1.7; respectively ($P=0.15$).	2
90. Koo BK, Erglis A, Doh JH, et al. Diagnosis of ischemia-causing coronary stenoses by noninvasive fractional flow reserve computed from coronary computed tomographic angiograms. Results from the prospective multicenter DISCOVER-FLOW (Diagnosis of Ischemia-Causing Stenoses Obtained Via Noninvasive Fractional Flow Reserve) study. <i>J Am Coll Cardiol</i> . 2011;58(19):1989-1997.	Experimental-Dx	103 patients	To determine the diagnostic performance of a new method for quantifying FFR with computational fluid dynamics applied to CCTA data in patients with suspected or known CAD.	56% of patients had ≥ 1 vessel with FFR ≤ 0.80 . On a per-vessel basis, the accuracy, sensitivity, specificity, PPV, and NPV were 84.3%, 87.9%, 82.2%, 73.9%, 92.2%, respectively, for FFR(CT) and were 58.5%, 91.4%, 39.6%, 46.5%, 88.9%, respectively, for CCTA stenosis. The AUC was 0.90 for FFR(CT) and 0.75 for CCTA ($P=0.001$). The FFR(CT) and FFR were well correlated ($r = 0.717$, $P<0.001$) with a slight underestimation by FFR(CT) (0.022 \pm 0.116, $P=0.016$).	2

**Chronic Chest Pain—High Probability of Coronary Artery Disease
EVIDENCE TABLE**

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
91. Norgaard BL, Leipsic J, Gaur S, et al. Diagnostic performance of noninvasive fractional flow reserve derived from coronary computed tomography angiography in suspected coronary artery disease: the NXT trial (Analysis of Coronary Blood Flow Using CT Angiography: Next Steps). <i>J Am Coll Cardiol.</i> 2014;63(12):1145-1155.	Observational-Dx	254 patients	To determine the diagnostic performance of noninvasive fractional flow reserve (FFR) derived from standard acquired coronary computed tomography angiography (CTA) datasets (FFR(CT)) for the diagnosis of myocardial ischemia in patients with suspected stable coronary artery disease (CAD).	The area under the receiver-operating characteristic curve for FFR(CT) was 0.90 (95% confidence interval [CI]: 0.87 to 0.94) versus 0.81 (95% CI: 0.76 to 0.87) for coronary CTA (p = 0.0008). Per-patient sensitivity and specificity (95% CI) to identify myocardial ischemia were 86% (95% CI: 77% to 92%) and 79% (95% CI: 72% to 84%) for FFR(CT) versus 94% (86 to 97) and 34% (95% CI: 27% to 41%) for coronary CTA, and 64% (95% CI: 53% to 74%) and 83% (95% CI: 77% to 88%) for ICA, respectively. In patients (n = 235) with intermediate stenosis (95% CI: 30% to 70%), the diagnostic accuracy of FFR(CT) remained high.	2
92. Min JK, Koo BK, Erglis A, et al. Effect of image quality on diagnostic accuracy of noninvasive fractional flow reserve: results from the prospective multicenter international DISCOVER-FLOW study. <i>J Cardiovasc Comput Tomogr.</i> 2012;6(3):191-199.	Observational-Dx	159 vessels in 103 patients	To assess the effect of CT quality on accuracy of FFR(CT) by comparing performance of FFR(CT) with severe stenosis by CT in relation to image quality; heart rate; signal-to-noise ratio (SNR); and common CT artifacts, including calcification, motion, and poor contrast enhancement.	On a vessel basis, accuracy of FFR(CT) was higher than CT stenosis for satisfactory or poor quality CTs (87.5% vs 64.6%), for heart rates > 65 beats/min (100% vs 52.9%), and for SNR less than the median (26.3) (84.4% vs 64.1%). Accuracy of FFR(CT) was superior to CT stenosis in the presence of calcification (85.7% vs 66.7%), motion (90.5% vs 57.1%), and poor contrast opacification (100.0% vs 71.4%). Similar relations were observed for exploratory analyses of FFR(CT) and CT stenosis on a patient basis. In 42 subjects who underwent coronary calcium scanning, accuracy of FFR(CT) was 77.8% (n = 18), 100% (n = 11), and 100% (n = 13) for coronary calcium scores of 0-100, 101-400, and >400, respectively.	2

**Chronic Chest Pain—High Probability of Coronary Artery Disease
EVIDENCE TABLE**

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
93. Norgaard BL, Gaur S, Leipsic J, et al. Influence of Coronary Calcification on the Diagnostic Performance of CT Angiography Derived FFR in Coronary Artery Disease: A Substudy of the NXT Trial. <i>JACC Cardiovasc Imaging</i> . 2015;8(9):1045-1055.	Observational-Dx	214 patients	To examine the diagnostic performance of noninvasive fractional flow reserve (FFR) derived from coronary computed tomography angiography (CTA) (FFRCT) in relation to coronary calcification severity.	Mean +/- SD per-patient and per-vessel AS were 302 +/- 468 (range 0 to 3,599) and 95 +/- 172 (range 0 to 1,703), respectively. There was no statistical difference in diagnostic accuracy, sensitivity, or specificity of FFRCT across AS quartiles. Discrimination of ischemia by FFRCT was high in patients with a high AS (416 to 3,599) and a low-mid AS (0 to 415), with no difference in area under the receiver-operating characteristic curve (AUC) (0.86 [95% confidence interval (CI): 0.76 to 0.96] vs. 0.92 [95% CI: 0.88 to 0.96]) (p = 0.45). Similarly, discrimination of ischemia by FFRCT was high in vessels with a high AS (121 to 1,703) and a low-mid AS (0 to 120) (AUC: 0.91 [95% CI: 0.85 to 0.97] vs. 0.95 [95% CI: 0.91 to 0.98]; p = 0.65). Diagnostic accuracy and specificity of FFRCT were significantly higher than for stenosis assessment in each AS quartile at the per-patient (p < 0.001) and per-vessel (p < 0.05) level with similar sensitivity. In vessels with a high AS, FFRCT exhibited improved discrimination of ischemia compared with coronary CTA alone (AUC: 0.91 vs. 0.71; p = 0.004), whereas on a per-patient level, the difference did not reach statistical significance (AUC: 0.86 vs. 0.72; p = 0.09).	2

**Chronic Chest Pain—High Probability of Coronary Artery Disease
EVIDENCE TABLE**

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
94. Douglas PS, Pontone G, Hlatky MA, et al. Clinical outcomes of fractional flow reserve by computed tomographic angiography-guided diagnostic strategies vs. usual care in patients with suspected coronary artery disease: the prospective longitudinal trial of FFR(CT): outcome and resource impacts study. <i>Eur Heart J</i> . 2015;36(47):3359-3367.	Experimental-Dx	584 patients	To test the hypotheses that patients with suspected CAD evaluated using a CTA/FFRCT-guided strategy would have fewer invasive angiograms that showed no obstructive CAD than would patients who were evaluated based on standard practice, and would have similar and low rates of major cardiac events.	Subjects averaged 61 +/- 11 years of age, 40% were female, and the mean pre-test probability of obstructive CAD was 49 +/- 17%. Among those with intended ICA (FFR(CT)-guided = 193; usual care = 187), no obstructive CAD was found at ICA in 24 (12%) in the CTA/FFR(CT) arm and 137 (73%) in the usual care arm (risk difference 61%, 95% confidence interval 53-69, P< 0.0001), with similar mean cumulative radiation exposure (9.9 vs. 9.4 mSv, P = 0.20). Invasive coronary angiography was cancelled in 61% after receiving CTA/FFR(CT) results. Among those with intended non-invasive testing, the rates of finding no obstructive CAD at ICA were 13% (CTA/FFR(CT)) and 6% (usual care; P = 0.95). Clinical event rates within 90 days were low in usual care and CTA/FFR(CT) arms.	1
95. Pouleur AC, le Polain de Waroux JB, Kefer J, Pasquet A, Vanoverschelde JL, Gerber BL. Direct comparison of whole-heart navigator-gated magnetic resonance coronary angiography and 40- and 64-slice multidetector row computed tomography to detect the coronary artery stenosis in patients scheduled for conventional coronary angiography. <i>Circ Cardiovasc Imaging</i> . 2008;1(2):114-121.	Observational-Dx	77 patients	To perform a head-to-head comparison of the diagnostic accuracy of the currently most advanced noninvasive state-of-the-art techniques for the detection of CAD, ie, WH-MRCA imaging versus 40- or 64-slice MDCT using conventional invasive coronary angiography as a reference standard.	According to the quantitative coronary angiography, 49 of 992 coronary segments >1.5 mm diameter had >50% diameter stenosis. MDCT had a higher success rate (100% versus 88%, P<0.001) and enabled identification of more segments (963 versus 726, P<0.001) than did WH-MRCA. On a per-segment basis, WH-MRCA had similar sensitivity (47/49 or 96% versus 48/49 or 98%, P=0.9) but significantly lower specificity (644/943 or 68% versus 863/943 or 92%, P<0.001) and accuracy (691/992 or 70% versus 911/992 or 92%, P<0.001) for the detection of >50% diameter stenosis than did MDCT. On a per-patient basis, the sensitivity was similar (17/17 or 100% versus 16/17 or 94%, P=0.9), but specificity (43/60 or 72% versus 53/60 or 88%, P=0.024) and diagnostic accuracy (60/77 or 78%, versus 69/77 or 90%, P=0.044) of WH-MRCA for the detection of >50% diameter stenosis were significantly lower than of MDCT.	2

**Chronic Chest Pain—High Probability of Coronary Artery Disease
EVIDENCE TABLE**

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
96. Alderman EL, Corley SD, Fisher LD, et al. Five-year angiographic follow-up of factors associated with progression of coronary artery disease in the Coronary Artery Surgery Study (CASS). CASS Participating Investigators and Staff. <i>J Am Coll Cardiol.</i> 1993;22(4):1141-1154.	Experimental-Tx	298 patients	To analyze five year follow up coronary angiography as part of the CASS.	For nonbypassed segments, right coronary artery and left anterior descending artery proximal and midlocations were associated with disease progression. For stenosis-containing segments, the initial severity, a non-left anterior descending artery location and increased treadmill duration predicted progression. Segment occlusion was associated with initial lesion severity, right coronary artery location and subsequent interval myocardial infarction. There were few predictors of progression or occlusion in bypassed arteries, other than initial lesion severity.	1
97. De Bruyne B, Pijls NH, Kalesan B, et al. Fractional flow reserve-guided PCI versus medical therapy in stable coronary disease. <i>N Engl J Med.</i> 2012;367(11):991-1001.	Experimental-Tx	1220 patients	The aim of this trial was to determine whether FFR-guided PCI with drug-eluting stents plus the best available medical therapy is superior to the best available medical therapy alone in reducing the rate of death, myocardial infarction, or unplanned hospitalization leading to urgent revascularization among patients with stable CAD.	Recruitment was halted prematurely after enrollment of 1220 patients (888 who underwent randomization and 332 enrolled in the registry) because of a significant between-group difference in the percentage of patients who had a primary end-point event: 4.3% in the PCI group and 12.7% in the medical-therapy group (HR with PCI, 0.32; 95% CI, 0.19 to 0.53; $P<0.001$). The difference was driven by a lower rate of urgent revascularization in the PCI group than in the medical-therapy group (1.6% vs 11.1%; HR, 0.13; 95% CI, 0.06 to 0.30; $P<0.001$); in particular, in the PCI group, fewer urgent revascularizations were triggered by a myocardial infarction or evidence of ischemia on electrocardiography (HR, 0.13; 95% CI, 0.04 to 0.43; $P<0.001$). Among patients in the registry, 3.0% had a primary end-point event.	1

**Chronic Chest Pain—High Probability of Coronary Artery Disease
EVIDENCE TABLE**

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
98. Fearon WF, Shilane D, Pijls NH, et al. Cost-effectiveness of percutaneous coronary intervention in patients with stable coronary artery disease and abnormal fractional flow reserve. <i>Circulation</i> . 2013;128(12):1335-1340.	Observational-Tx	888 patients	To evaluate the economic and quality-of-life outcomes in the FAME 2 trial.	Initial costs were significantly higher for PCI in the setting of an abnormal fractional flow reserve than with medical therapy (\$9927 versus \$3900, P<0.001), but the \$6027 difference narrowed over 1-year follow-up to \$2883 (P<0.001), mostly because of the cost of subsequent revascularization procedures. Patient utility was improved more at 1 month with PCI than with medical therapy (0.054 versus 0.001 units, P<0.001). The incremental cost-effectiveness ratio of PCI was \$36 000 per quality-adjusted life-year, which was robust in bootstrap replications and in sensitivity analyses.	1
99. Tonino PA, De Bruyne B, Pijls NH, et al. Fractional flow reserve versus angiography for guiding percutaneous coronary intervention. <i>N Engl J Med</i> . 2009;360(3):213-224.	Experimental-Tx	1,005 patients	To compare treatment based on the measurement of FFR in addition to angiography with the current practice of treatment guided solely by angiography in patients with multivessel coronary artery disease for whom PCI is the appropriate treatment.	The mean (+/-SD) number of indicated lesions per patient was 2.7+/-0.9 in the angiography group and 2.8+/-1.0 in the FFR group (P=0.34). The number of stents used per patient was 2.7+/-1.2 and 1.9+/-1.3, respectively (P<0.001). The 1-year event rate was 18.3% (91 patients) in the angiography group and 13.2% (67 patients) in the FFR group (P=0.02). Seventy-eight percent of the patients in the angiography group were free from angina at 1 year, as compared with 81% of patients in the FFR group (P=0.20).	1

Evidence Table Key

Study Quality Category Definitions

- *Category 1* The study is well-designed and accounts for common biases.
- *Category 2* The study is moderately well-designed and accounts for most common biases.
- *Category 3* There are important study design limitations.
- *Category 4* The study is not useful as primary evidence. The article may not be a clinical study or the study design is invalid, or conclusions are based on expert consensus. For example:
 - a) the study does not meet the criteria for or is not a hypothesis-based clinical study (e.g., a book chapter or case report or case series description);
 - b) the study may synthesize and draw conclusions about several studies such as a literature review article or book chapter but is not primary evidence;
 - c) the study is an expert opinion or consensus document.
- M = Meta-analysis

Dx = Diagnostic

Tx = Treatment

Abbreviations Key

ASIR = Adaptive statistical iterative reconstruction

AUC = Area under the receiver operating characteristic curve

CAD = Coronary artery disease

CCTA = Coronary computed tomography angiography

CI = Confidence interval

CMR = Cardiac magnetic resonance

CT = Computed tomography

CTA = Computed tomography angiography

CTP=Computed tomography myocardial perfusion imaging

DECT = Dual energy computed tomography

ECHO = Echocardiography

FDG-PET = Fluorine-18-2-fluoro-2-deoxy-D-glucose-positron emission tomography

FFR = Fractional flow reserve

HR = Hazard ratio

MDCT = Multidetector computed tomography

MPI = Myocardial perfusion imaging

MRA = Magnetic resonance angiography

MRI = Magnetic resonance imaging

MRP = Magnetic resonance perfusion

NPV = Negative predictive value

PCI = Percutaneous coronary intervention

PET = Positron emission tomography

PPV = Positive predictive value

ROC = Receiver operating characteristic

SPECT = Single-photon emission computed tomography